NEWER CONCEPTS IN INTESTINAL BACTERIOLOGY *

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Scientific advances are subject to constant cyclic changes reflecting the fluctuating interest in a particular problem with progression of time. Not so long ago, intestinal bacteriology might have been regarded as a closed chapter with little hope for new findings; however, recent observations have changed this outlook, providing renewed impetus for research. The purpose of this paper is to point out some of these new developments.

Fecal Population

Misconceptions obscured the quantitative as well as the qualitative aspects of intestinal bacteria. Mainly due to technical inadequacies, a complete recovery of all organisms dispersed in stool has not been possible. In fact, as long as only aerobic culture methods were used, the discrepancy between comparative cell counts of stained smear preparations and live cultures was so great that less than 5% of the former cells were found to be growing in culture. This led to the erroneous conclusion that the majority of excreted bacteria are not viable.

Now, by combining aerobic and anaerobic culture methods, by using selective and enrichment media, and by extending the incubation time, more than 75% of the organisms can be recovered alive. It has been found preferable to relate the bacterial count to dry weight instead of wet weight, since the fluid content of stool is extremely variable.

As far as we know, the number of bacteria in feces is influenced by a variety of factors: the type of food consumed, the amount of unresorbed nutrients, the motility and secretory function of the intestines and the varied fluid exchange. In addition, the length of time the stool is retained in the colon has also a definite bearing on the findings. Hence, it should not be surprising that individual differences, as well as differences in the same person at different times, have been noted. Such constant fluctuation of the bacterial population complicates greatly the composite picture. As we shall see later, all these organisms coexist in a continuous struggle for survival and it is by no means clear as yet to what extent the host is benefited or harmed by their presence.

The qualitative aspects have also undergone a significant revision. Whereas formerly it was believed that the Gram

negative coliforms are the chief components of feces, now we know that they represent only about 1-10% of the total fecal bacteria. The remaining 90% of the organisms have not received nearly as much attention as they deserve. The reason for this incongruity was that easier growing and less exacting bacteria (such as the coliforms) are apt to overgrow and suppress some of the other bacteria which might be present; hence, the laboratory findings do not necessarily reflect the true composition of intestinal inhabitants.

Then, we learned to distinguish between "resident" strains and "transient" strains. This does not only refer to the persistence or evanescence of diverse organisms but to the prevalence of specific serological types of the same organism.

Intrinsic Bacteria

A most interesting advance came about from the intensified study of intrinsic bacteria. Whereas in earlier investigations the emphasis was in accordance with Koch's postulates — aimed at recovering some extrinsic pathogens and establishing their causal relationship to a particular disease — in many of the more recent works, intrinsic bacteria (like **E. coli**) were scrutinized with regard to their pathogenic potentialities.

It was Kauffman and many of his followers who skillfully demonstrated that, of the large number of coliforms, there are some serologically distinct types which are causally related to disease (e. g., infant diarrhea). Some of these types are also known to assume pathogenicity outside the intestinal tract (bladder infection, gallstone formation). At last, the hopeless confusion which surrounded the pathogenic role of coli bacteria was lifted.

This started a new trend in research which was extended to other intestinal inhabitants. Among these, the intestinal streptococci, particularly "Enterococci," received increasing attention. Like the coliforms, they also are considered indicative of water polution and have been frequently implicated in outbreaks of food poisoning. Since, however, Enterococci are normally present in the gut, it

is difficult to ascertain their pathogenicity unless evidence for the existence of species differences with unequivocal pathogenic properties could be established. But in this instance, serology has, thus far, not proven to be successful, and the ability to produce large amounts of tyramine by certain strains (**Gale**) could not be correlated with disease.

Still, it is remarkable that occasionally one can cultivate from strongly acid and loose stools a pure culture of Enterococci with few or no coli organisms present. It would seem that, in such cases, the shift in organisms may be due to changes in milieu resulting in digestive disturbances. On the other hand, there have been reported outbreaks of infant diarrhea from England and Germany in which the preponderance of **Strep. liquefaciens** was established beyond doubt. The significance of these organisms requires further study.

Much less understood than either one of the aforementioned groups are organisms belonging to the **Proteus, Pseudomonas** and **Alcaligenes faecalis** families. They have been recovered in cases of acute gastroenteritis, in obstipations due to putrefaction and quite frequently after treatment with antibiotics. However, they have also been found in geriatric patients without any disease-producing effects. Especially **Proteus rettgeri** and **Proteus morganii** are worth watching in future investigations.

Since the anaerobic techniques have been improved, the Gram negative nonspore forming anaerobes and the Gram positive spore formers have been studied more extensively. The **Bacteroides,** for instance, were found to outnumber the aerobic flora in the colon and are not infrequently associated with ulcerative processes of the mucous membranes (chronic colitis ulcerosa). The evidence, however, for their causative role is by no means conclusive. It seems rather that hypersecretion and stagnation **per se** will favor their rampant growth in the intestines. Newly recognized is the fact that special types of **Clostridia welchii** can provoke acute food poisoning and that elaboration of SH_2 by

clostridial organisms is a clear indication of a pathogenous trait.

Lactobacillus Problem

Considerable amount of work was devoted to lactobacilli. Particularly the **L. bifidus** problem attracted the interest of pediatricians. Whereas formerly it was believed that the Bifidus is unique for the stool of breast-fed infants, it has been found lately that it can be recovered, though to lesser extent, from the feces of bottle-fed babies, children, and even adults. Careful analysis of their striking prevalence in breast-fed infants revealed that two "bifidogen" principles are responsible for their growth: the carbohydrate "lactulose" as an essential nutrient (Petuely), and a protein-carbohydrate ratio favorable for their implantation. Both factors are apparently optimal in the breast-fed infants; nevertheless, they are not entirely absent in the other age groups either. The controlling effect of lactobacilli in the maintenance of proper intestinal balance will be discussed shortly.

Bacterial Distribution

New concepts have arisen with regard to the topographic distribution of bacteria in the intestinal tract. We have known for some time that it is essential to our general well-being that proteolytic and fermentative organisms keep a proper equilibrium, but what we have less commonly known is that the relative composition of the resident flora is variable at different levels of the gut. The reason that earlier observations failed to recognize this fact was mainly technical. Most conclusions of the past were based on fecal findings or autopsy material. There have been sporadic attempts to get material from other sites of the intestines, but it is difficult even today to obtain such samples in the living host without undesirable contaminants.

Quite recently, a gadget consisting of a cartridge and attached to a Levine tube has been introduced which could be opened or closed at will in any desired topographical location under the control of hydraulic pressure. It was found that, contrary to former belief which has taken for granted the sterility of the duo-denum and jejunum, these upper parts of the intestine are also inhabited by bacteria (chiefly lactobacilli). This may have profound influence on the exchanges which take place across the intestinal walls. Then, as we go further down in the gut, gradually the Gram negatives assume preponderance. This is in conformity with the fact that all bacteria have their own individual requirements but, at the same time, are subject to the control of the changing environment which characterizes the various sections of the intestine.

Interaction Among Intestinal Bacteria

Special problems arise and often complicate the picture in the gut as a result of the mutual influence which the component members of a variable mixture of organisms exert on each other. They promote or inhibit one another in their life processes. For instance, there can be little doubt that microorganisms with rapid oxygen consumption will pave the way for the growth of microaerophilic or anaerobic bacteria. Similarly, various metabolic products, including vitamins elaborated by certain bacteria, may be beneficial to some or harmful to others. As intimated earlier, by keeping mutual check, a state of balance is maintained under normal conditions. This explains how lactobacilli, due to stronger acid production from sugar, can curb the coliforms, or conversely how coliforms can overcome lactic acid bacteria by utilizing putrefactive processes more efficiently. Similar antagonisms exist among many other organisms.

However, such biochemical competition is not the only way of interaction. It is not unusual that metabolic products of antibiotic nature are formed which exert an inhibitory effect on the ecology of the microbial population. Among these, perhaps "Colicine" has been most intensively studied in preceding years. Recent observations seem to indicate that the extreme instability of the intestinal flora is partly linked to the appearance and disappearance of antibiotically active coli strains in feces and that besides coliforms other organisms are also capable of producing colicine-like agents.

The significance of these findings is still obscure.

A different kind of interaction has been discovered during convalescence from dysentery between Coli and Shigella strains. It has been observed that coli strains became agglutinable by sera prepared against Shigella organisms. At first, some simple antigenic relationship was suspected among these bacteria, but, more recently, evidence has been forthcoming that transduction — i.e., gene transference by lysogenic phages — is responsible for the phenomenon. Other examples have also been reported. However, the occurrence is comparatively rare and has not impaired the principle of group or type specificity in bacteriology.

The great expectations connected with bacteriophage treatment in cholera have not materialized in other intestinal infections; still, there are many as yet unsolved problems in which bacteriophage may play a prominent part. It cannot be accidental that the appearance of bacteriophage in feces usually coincides with the turning point in the course of the disease. Since bacteriophage activity is specific, some kind of cause and effect relationship cannot be easily dismissed.

Host-Parasite Relationship

In spite of concerted effort, it is only partially understood how the ecology of bacteria in the intestine develops and why it varies at times. A proper answer to such questions might determine the conditions which are necessary for the successful implantation of a desirable flora in opposition to an undesirable one. Some favorable claims to that effect have not been substantiated, or, at best, they were of short duration only.

Among the known factors which affect the ecology, nutrition and its effects on the digestive glands and intestinal peristalsis play a major role. However, there may exist some additional controlling mechanisms of which we know very little. It would seem that the slightest derangement in digestion is capable of altering the distribution of bacteria and thereby extending them into areas where they are not supposed to be normally present. Such areas may be vulnerable

to attack and open to permeation. A more or less severe interaction between host and bacteria may result in antibody stimulation. The response of the host could provide important information concerning auto-infections of obscure origin.

Unfortunately, only a few trials were carried out to test the immunological reaction of the host to bacteria of his own indigenous flora. For instance, one could find out whether intestinal bacteria or their breakdown products are in part responsible for the maintenance of adequate resistance. One might speculate that a constant flow of stimuli is keeping the immune mechanisms incited. This contention, however, needs further validation.

One also might ask: are bacteria to any significant degree involved in essential vitamin synthesis which could benefit the host? Claims to this effect have been greatly exaggerated, especially since it is known that vitamin producing bacteria are also great consumers of vitamins. From newer investigations it is evident that the vitamin deficiencies observed following administration of antibiotics are not so much due to the action of these agents on bacteria, **per se,** as rather to direct changes affecting mucosal absorption.

It would seem that an up-to-date appraisal of the host-parasite relationship is as yet confronted with considerable difficulties. On one hand, one knows that life without bacteria has become a laboratory accomplishment of great significance; on the other hand, it is doubtful whether in real life one could exist without their presence. It is also a moot question whether or not in final analysis any real benefit does accrue to the host during this symbiotic interplay.

Some Chemotherapeutic Considerations

A brief appendage of this aspect seems justified not only because it contributed effectively to the combating of intestinal infections, but also because it created unexpected problems of grave importance. Since the broad spectrum antibiotics, which are commonly used, have been introduced, it became possible in

most cases to reduce the intestinal population to practically nil. This procedure has been used successfully to eliminate bacteria in preparation for intestinal operations. The achieved effect, however, is only of short duration and at times equivocal. Similarly, the use of antibiotics postoperatively in prophylactic treatment has had its failures. One should, therefore, abstain from using antibiotics indiscriminately in uncomplicated cases without special indication (e.g., intestinal perforation).

Usually, the shift in microbial composition after antibiotics is reversible without any harm to the host; but occasionally undesirable effects may result with more or less serious consequences. Since, unfortunately, there is no way to foresee such events, their occurrence can seldom be prevented.

The most alarming ill effects are related either to the rampant growth of antibiotic-insensitive, or to the selective development of antibiotic-resistant microorganisms. During hospitalization of patients, it is not unusual to incur an intractable enterocolitis caused by Staphlococci, Coli or Enterococci, and the term "Hospitalismus" was coined to describe its focal origin and rampaging nature. In extreme cases practically pure cultures of these bacteria can be isolated from the stool long before the clinical symptoms become evident. Then, it is rather common to find nowadays that under the influence of antibiotic treatment, yeasts like **Candida albicans** will displace the entire intestinal flora. Particularly in patients with lowered resistance, including diabetics, this could become quite ominous.

Conclusion

From what has been said in this brief review, it should be clear that the problems of intestinal bacteriology are highly complex and variegated. Many questions of importance are not even touched. However, this presentation amply illustrates the fast changing concepts of this topic in recent years.

IRON METABOLISM

A Review of Biochemical Mechanisms and Their Clinical Implications

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Ionic iron is one of the most essential, yet potentially toxic, minerals in mammalian physiology. It not only acts as an enzymatic cofactor, but it is an important component in intracellular respiratory enzymes. Iron-containing compounds can be divided into two general categories. The porphyrin group is represented by hemoglobin, myoglobin, and the heme enzymes. The non-porphyrin group is represented by siderophilin, ferritin, and hemosiderin.[1]

Approximately 67% of the total body iron is contained in hemoglobin. Twenty to twenty-five milligrams of iron is released daily by physiological hemolysis and re-utilized by the marrow in the production of fresh erythrocytes.[2]

Myoglobin and the heme enzymes are utilized in the complicated process of intracellular oxidation which occurs in the mitochondria of the muscle cell. Hydrogen atoms are removed in the oxidation of substances in the citric acid cycle and are transported by the cytochrome enzymes to an oxygen source where water is the end product.[3]

Siderophilin (transferrin) is a pseudo-globulin of 90,000 molecular weight. Each molecule contains two iron atoms in the ferric (trivalent) state with five unpaired electrons in the outer shell.[4] Si-

derophilin accounts for 3% of total plasma protein and behaves physiochemically as an albumin or an alpha globulin. The normal serum iron contained in siderophilin is 100 to 120 gamma per 100cc of serum. The total iron binding capacity of the circulating siderophilin is 300 gamma per 100 cc of serum.

Crystalline ferritin contains surface sulfhydryl groups which bind ionic trivalent iron with three unpaired electrons. It is believed that this surface ionic iron can be released by reducing substances, such as glutathione, and transferred to siderophilin. The trivalent iron (three unpaired electrons in outer shell) is reduced by such substances as glutathione to the bivalent state. This bivalent iron enters the circulation and is autoxidized to the special trivalent iron in siderophilin, which has five unpaired electrons in the outer shell.

Ferritin is an iron-containing protein, first isolated from horse spleen by Laufberger in 1937. It consists of an ellipsoidally constructed protein called apoferritin. Micelles of ferric hydroxide are attached to the surface of the apoferritin molecule. These micelles have an average composition of $(FeOOH)_8(FeOPO_3H_2)$ and contain twenty-three percent of iron by weight.[1] Theoretically, three types of trivalent iron compounds are possible on the basis of the number of unpaired electrons which ferric iron may possess in the

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outermost electron shell. The most common types are those containing one or five. The rarest form is ferric iron with three unpaired electrons per atom, a form which has been identified in ferritin. These various forms of iron are determined by making magnetic measurements as described by Michaelis.[5]

Because of the inability to duplicate the ferritin type of iron micelle in vitro, it is strongly suspected that polymerization of these iron hydroxide units, and their attachment to apoferritin, is mediated by some enzyme activity.

The functions of ferritin are numerous and complex. It is the normal form of iron storage in the spleen, liver, and bone marrow, and the regulator of iron absorption by the mucosal cells of the gastrointestinal tract and cells in the placenta. When the concentration of ferritin (actually controlled by the quantity of apoferritin synthesis) is at a high level in the gastrointestinal tract and placenta, it is believed that further iron absorption is reduced or completely prevented.[5] The role of ferritin in the production of irreversible shock and hypotension has been suggested by the experimental evidence that small amounts of ferritin, in the presence of adrenalin, will inhibit the vasoconstrictor action of the latter on the terminal arterioles of the rat meso-appendix. Ferritin has therefore been described as the hepatic vasodepressor material.[6]

Hemosiderin is a granular substance which contains clusters of iron hydroxide units mixed with apoferritin. The clusters are large enough to be microscopically visible and stainable. Total content of trivalent (ferric) iron of the three unpaired electron type may reach 35% by weight. Hemosiderin is probably formed by the same method of polymerization as ferritin, with the exception that the iron micelles become abnormally large and cross links occur, uniting several ferritin molecules.[1]

Iron Absorption

Iron absorption is influenced by enzyme activity of the mucosal cell, location, lumen environment, erythroid activity, and condition of the iron stores. The reducing systems of the mucosal cell are pictured as converters of trivalent iron

in the three unpaired electron state to the trivalent iron of siderophilin in the five unpaired electron state.[6,7] The main location of iron absorption is the duodenum, where the acid pH allows reduction of ferric ions by ascorbic acid and cysteine. The resulting product, ferrous iron, can then be absorbed. The presence of ascorbic acid increases absorption from 10 to 20%. The presence of phosphates, phytates, coeliac disease or idiopathic steatorrhea will decrease iron absorption.

In iron deficiency states, absorption of iron will be high, but serum iron and iron stores will be low. The serum iron, iron stores, and iron absorption are all high in pernicious anemia, pyridoxine deficiency, and hypoplastic anemias because hemoglobin synthesis is depressed due to a deficiency of specific nutritional substances or to toxic effects. Iron absorption will be increased in chronic inflammatory states, but the serum iron will be low because iron is being taken up by the storage depots and tissues. Bone marrow activity and hemoglobin synthesis are also depressed in these states.

Iron Storage Diseases

Diseases associated with excessive iron storage have been classified into idiopathic and acquired hemochromatosis and hemosiderosis.

Historically, the etiology of **idiopathic hemochromatosis** has been based on the postulated presence of a mucosal absorptive defect arising as a genetically controlled inborn error of metabolism. From experimental studies, the major concensus is that this genetic control is mediated by an autosomal gene of incomplete penetrance transmitted as a Mendelian dominant with varying expressivity.[2,10] In idiopathic hemochromatosis, it is estimated that 2 to 5 milligrams of excess iron are absorbed daily, thus requiring twenty to forty years for abnormal iron stores to develop. These massive accumulations of iron, as ferritin and increased deposits of melanin, lipofuscin, and hemofuscin, are associated with severe fibrosis of the liver and pancreas in man.

Recent enzyme investigations by Green and Mazur on normal rat liver incubated in Ringer's solution resulted in the isolation of uric acid. Uric acid has the capa-

bility of reducing ferritin and releasing ionic iron. Since production of uric acid is controlled by the enzyme, xanthine oxidase, it is convenient to theorize a mechanism for possible genetic control.[13]

It is extremely important to point out that the pathophysiology of these diseases has not been definitely substantiated. Many investigators feel that there is not adequate proof to attribute tissue damage solely to the presence of excess iron. For support of their views they point out the lack of tissue damage in cases of hemosiderosis and in animals who have been experimentally treated with large doses of intravenous iron over a two year period.[2,11] Investigators taking the opposite argument point out the occurrence of definite tissue alterations in cases of transfusion hemochromatosis, and clearly correlate these tissue changes with the clinical symptoms of hepatic, pancreatic, and cardiac pathology. These tissue changes cannot be logically explained by the mechanisms of other chronic diseases which may be present in the same patient.[12]

Acquired hemochromatosis can be mediated by excessive dietary intake of iron or by excessive use of blood transfusions. In the dietary type of hemochromatosis, as exemplified by the Bantu native, two to ten milligrams of excess iron may be absorbed daily.[9] The symptoms of the disease may not appear for twenty to forty years, and they are also related to other factors, such as a high ethanol intake and a deficient diet. In transfusion hemochromatosis, 25 to 30 milligrams of excess iron may be liberated from each 500 cc of blood given. This liberated iron is in addition to the 25 milligrams of iron from daily physiological hemolysis and may cause symptoms to appear within 5 years.[12]

Hemochromatosis versus Hemosiderosis

Separation of these two conditions was concisely defined by Finch and Finch and reviewed by MacDonald.[2,15] First, it has been believed that there are three important morphological differences between hemochromatosis and hemosiderosis. The cellular distribution of iron in hemosiderosis is in the reticuloendothelial cells as opposed to the parenchymal cells for hemochromatosis. Iron content of the bone marrow, kidney and spleen is much higher in the former disease. The incidence of cirrhosis and pancreatic fibrosis is much higher in hemochromatosis. However, MacDonald has done much to dilute these arguments for separation of these diseases by his autopsy study, which shows that idiopathic hemosiderosis and idiopathic hemochromatosis occur equally and the separation on a morphological basis is an arbitrary one.[15] The other theoretical bases for the separation of these diseases, such as the postulated presence of an "inborn error" of iron metabolism in hemochromatosis; the concept of a mucosal block to the absorption of iron in normal persons with alteration of the block in hemochromatosis; and the assumption that iron causes or contributes to cirrhosis in the liver, have been intensively studied and cannot be substantiated. MacDonald concludes that there should not be a separation and that iron storage diseases are caused by abnormal intermittent absorption of iron from the diet, conditioned by nutritional and disease factors. He summarizes evidence for his view that hemochromatosis is a variant of portal cirrhosis and idiopathic hemosiderosis as follows:

1) Hemochromatosis is more often associated with portal or nutritional cirrhosis than with other types of cirrhosis.[17]

2) Portal cirrhosis and hemochromatosis merge in terms of the amount and location of iron in various organs, and the cirrhosis is identical.[16]

3) There is a poor nutritional history in many cases of hemochromatosis.[17,18,20]

4) Alcoholism is found in 29% to 85% of cases and is another index for poor nutrition.[17]

5) Idiopathic hemosiderosis is found more often and with greater quantities of iron in the tissues in portal cirrhosis suggesting that there is abnormal absorption or tissue binding of iron.[16]

6) The same diet in rats which produces cirrhosis causes excess iron deposits in the liver, due to either greater absorption or tissue deposition.[19]

7) Pancreatic fibrosis is found in uncomplicated portal cirrhosis in approximately 85% of cases.[17,21]

Clinical Manifestations

Hemochromatosis is recognized in large major hospitals approximately once in twenty thousand admissions. In specialty centers for diabetics, it is ten times greater in frequency. The majority of cases, with exception of those occurring among the Bantus, give no history of excessive dietary intake of iron. Ninety percent of all cases occur in males, because females are protected by menstrual iron losses.

Hepatic enlargement occurs in 80 to 90% of all cases. The incidence of primary carcinoma of the liver in cases of hemochromatosis is 14%. This is much higher than the incidence of primary carcinoma in Laennec's cirrhosis. During the late stages of hemochromatosis, the serum iron is oversaturated, with levels of 300 to 3100 gamma per 100 cc of serum. Pigmentation of the skin is due to the increased deposits of melanin (bronze) and iron (metallic gray). There is usually evidence of palmar erythema, atrophy, and spider angiomata. Congestive heart failure is one of the leading causes of death.[2]

Iron Poisoning

Deaths due to ingestion of large quantities of medicinal iron have occurred mainly in children. High concentrations of iron will cause a serious clinical picture manifested by vomiting, shock, and coma. Apparently there is loss of control of absorption, and large quantities of ferritin are formed or liberated. Autopsies have revealed edema, ulceration of the stomach, mild pulmonary edema, and visceral congestion.[14]

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VENOUS THROMBOSIS: A CRITIQUE

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When one considers unfortunate experiences in the practice of medicine, one must put the occurrence of pulmonary embolism at the top of the list. None of us have been spared the experience of having one of our patients die suddenly and at post-mortem finding a large clot in either of the pulmonary arteries.

The reports of the incidence of pulmonary embolism are quite interesting. Two per cent of all patients going to the hospital will die post-operatively. Of these, six to ten per cent die of some thromboembolic disease. The major source of these pulmonary emboli is peripheral, over ninety per cent, as a matter of fact. Thus, any cardiac origination is quite minor. Of these ninety per cent which arise from a peripheral source, seventy-three per cent occur in the large veins of the thigh and the pelvis. Eight per cent occur in the smaller veins of the leg. Therefore, in considering the most important aspects of the prevention of emboli, the study of thrombotic disease of the pelvis and the extremities is mandatory.

As the reader notices, the absence of a reference to aseptic thrombophlebitis, as a term, is evident. There is a hazard and a fallacy in reasoning in trying to differentiate between aseptic forms of phlebothrombosis and thrombophlebitis. This is now being emphasized very strongly in the literature.[2] These entities really represent different phases of the same disease. The pathologists have repeatedly shown that there is no histological basis for differentiation of a venous thrombosis. If one does microscopic sections through the tail of a "thrombophlebitis" he will find that he is diagnosing "phlebothrombosis," for there will be no inflammatory reaction about the vein. However, if the microscopic section is done further distally, toward the adherent part of the thrombus, one will find microscopic evidence of a "thrombophlebitis."

We can also see a fallacy in the belief that patients with thrombophlebitis are secure against pulmonary embolism. This belief in differentiation is not only valueless but dangerous. Treatment must be instituted in both, and both must be considered one entity: venous thrombosis. Now, with this fact in mind, let us consider the causes of venous thrombosis.

Basic Tenets

Virchow, over 100 years ago, proposed three basic etiological tenets of venous thrombosis:

1. Trauma to the vein wall.
2. Venous stasis.
3. Changes in the coagulability of the blood.

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These have not changed very much. Aschoff has added one other tenet: changes in the corporal elements of the blood. Practically all causes of venous thrombosis can be classified under these basic tenets.

For example, let's take the first tenet, which is trauma to the vein wall. Under causes of trauma to the veins we find degenerative diseases, acute trauma such as venipuncture and prolonged transfusions, and surgical trauma.

The second tenet is venous stasis. Venous circulation depends upon the arterial blood flow, the abdominal and leg muscle pumps, negative intrathoracic pressure, and decreased intra-abdominal pressure. Anything that will affect these factors will predispose to venous stasis. For example, with decreased arterial flow, patients who have heart failure, myxedema, arteriosclerosis obliterans, or dehydration will be more prone to thrombotic disease. The second component in venous stasis is a decrease in abdominal and lower extremity muscle pump action. This occurs in any patient who is at bed rest, such as post-operative patients who have any form of long inactivity.

During the war, persons who remained in cramped air raid shelters for a long period of time showed an increased incidence of pulmonary embolism. Individuals who take long automobile rides, such as truckers, are prone to get pulmonary embolism. Interestingly enough, one of our modern cultural activities, television viewing, has increased the incidence of venous thrombosis. Elderly individuals sit in one position for a long period of time. They usually sit with their legs akimbo, develop stasis in the lower extremities, and will certainly develop thrombosis.

Emphysema, pulmonary fibrosis, and splinting of the chest wall will decrease the negative intrathoracic pressure, and decrease the suction effect on the veins of the abdomen. Increased intra-abdominal pressure, such as found with pregnancy or tumors impinging upon the veins of the pelvis, or with tight binders, will increase the venous stasis of the lower extremities. Another factor is the valves of the veins, which aid in return-

ing the blood to the right heart. If these valves are incompetent, there will be an increased pressure within the vein and stasis will occur. Of all the causes of venous thrombosis, venous flow retardation, or stasis, is considered the most important.

The third tenet is changes in coagulability of the blood. These are constitutional defects of which we know very little. They are defects, such as increases in thrombocytes or decreases in fibrinolysins, which will increase the clotting of the blood. There are diseases which are known to have increased clotting. Patients with carcinoma of the gastrointestinal tract, statistics show us, have twice as much thrombosis as a group without carcinoma.

Pathogenesis of the Thrombus

In describing how thrombosis takes place, Quick has shown that venous thrombosis is initiated by an intimal injury, with a localized liberation of tissue thromboplastin to produce a clot attached to the area of the injury. When this clot retracts, a serum rich in thrombin is expressed. With good circulation this serum is rapidly diluted and is swept into the blood stream. However, if the blood flow is sluggish, the thrombin causes the formation of a secondary clot attached to the primary thrombosis. Repetition of this process accounts for the growth of a clot in the direction of the blood flow. This theory is compatible with Virchow's tenets.

Aspects of Treatment

When discussing the treatment of venous thrombosis, one must consider two aspects: the preventive and the definitive treatment. In venous thrombosis prophylaxis, we can organize our discussion again along the guidelines of Virchow's basic tenets.

First, how can we prevent the intimal damage? There is no way known, at the present, to prevent **internal** intimal damage, i.e., the damage which is caused by degenerative diseases. However, one can prevent **external** intimal damage. For instance, the use of the lower extremities for infusions and cut-downs should be condemned. By inserting a needle into these veins we have satisfied the first

tenet of Virchow for formation of thrombosis: the intimal damage. Then, by keeping the extremity at rest, in that we do not allow the patient to move his extremity when he has an infusion running, we are satisfying the second tenet, which is production of venous stasis by loss of the muscle pump.

The same, I feel, is true for the upper extremities, except that, in using the smaller veins of the hands, we allow the patient to move his arm around, and therefore the incidence of venous stasis in the arm is much less.

In doing surgery, a surgeon should be guided by the basic principle of gentleness in handling tissue and thus he will be doing much less damage to the veins of the leg.

The "Stir-up" Regime

The second factor, which is the venous flow retardation, or stasis, has been answered by a "stir-up" regime which has been organized in most good institutions. It consists of:

1. Early ambulation.
2. Use of toe and leg exercises.
3. A condemnation of the position of the flexed knee and inguinal areas, to insure that there will be no obstruction to the veins in these areas. The best plan, of course, would be to elevate the legs slightly without any flexion of the knee, ankle or inguinal areas.
4. Deep breathing exercises, in order to increase the negative intrathoracic pressure.

Another factor which must be treated in order to obviate venous stasis is dehydration. Rehydration of the patient will decrease any increased viscosity of the blood. The doctor must treat any polycythemic factor. One must be sure that there is a good cardiac output which, of course, brings up the subject of digitalization.

In discussing coagulation ability one must consider the use of prophylactic anticoagulants in patients going to surgery or remaining in bed for long periods of time. Coon and Collar have discussed "thrombosis prone" patients. Examples of these are the hypertensives; the patients with previous venous disease; and the patients with coronary disease, obesity, malignancies, and those who remain in bed for prolonged periods of time. The contention is that these patients should be put on prophylactic anticoagulants before going to surgery and continued on this therapy indefinitely after surgery.

Definitive Treatment

In the definitive treatment of venous thrombosis, there are two aspects which must be considered: the local and the general.

In the **local** aspect, if there is no arterial insufficiency, moist warm packs may be placed on the patient from the groin to the ankle. Elevation of the leg thirty degrees is helpful. Elastic stockings may be used. Sedation is used for pain during the first few days and, if necessary, paravertebral blocks are used. It has been my experience that, when there is a concomitant arterial spasm, paravertebral blocks are quite effective. As a matter of fact, they dramatically relieve the pain which accompanies these severe spasms. Antibiotics are not to be used, generally or locally, but should be used if the diagnosis is a septic type of thrombosis. The use of anti-inflammatory agents, such as trypsin, streptodornase, and streptokinase, have not, in my experience, been effective.

Two Parts of Therapy

The **general** therapy of a venous thrombosis can be divided into two sections: 1) anticoagulants and 2) surgery.

Anticoagulants commonly used are heparin, coumadin and fibrinolysin. Heparin is used in the acute phase in venous thrombosis because of its antiinflammatory effect as well as its anticoagulant effect. Later, the coumadins may be used. The coumadin used depends on the physician's personal experience. The use of fibrinolysin has been reviewed from the original work by Moser to a present survey done by Warren. Warren found that extensive amounts of fibrinolysin must be used: up to 150,000 units of the material every hour for twelve to twenty hours from the onset of thrombosis. Fibrinolysin should not be used after the thrombus

has organized. It must be used within six to seven hours from the onset of thrombosis to get any effect. Further work on this material must be done, for there have been some definite untoward reactions with these materials.

Surgical Controversy

Surgery consists of proximal venous interruption. There is controversy in the use of surgery because surgical ligation of superficial or common femoral veins does not appear to be basically sound, since half the thrombi are in a location where bilateral procedures would have to be done. Again, if the statistics which were mentioned in the beginning of this paper are considered, 73% of the thrombi are found in the large veins of the thigh and the pelvis. Therefore, if any type of ligation is to be effective, it would have to be at the inferior vena cava. This ligation is a drastic procedure, and is still fraught with many sequelae which are not palatable to the patient or surgeon. There are, however, indications for inferior vena cava ligation. The indications are:

1. Failure of anticoagulation therapy (recurrent emboli).
2. Septic emboli.
3. Contraindications to anticoagulants, as in areas of extensive surgical dissection, such as abdomino-perineal resections and radical breast surgery.

In the opinion of most workers (medical and surgical) in this field, the use of anticoagulants should be the primary therapy in the treatment of venous thrombosis. If, however, anticoagulants do not prevent embolization, then inferior vena cava ligation is indicated.

Acute Phase Therapy

It takes seven to ten days for the acute phase of venous thrombosis to pass.

During this time elastic supports are applied to the extremities in order to support the superficial system of veins and to prevent edema. These supports are necessary until the damage to the deep system is repaired. The edema is a factor in causing the skin changes of the postphlebitic syndrome by interfering with capillary flow. We continue anticoagulants if necessary, especially in those patients who have continuing phlebitis. With the prophylactic principle in mind, anticoagulation therapy can be continued indefinitely.

Unfortunately, in spite of good therapy, a number of these patients go on to the chronic phlebitic syndrome. This is characterized by marked fibrosis of the subcutaneous tissue, with ulceration and an elephantiasis type of edema distal to the venous obstruction. These patients should have continuous elastic support. Elevation of the leg should be suggested several times daily. Good foot hygiene and immediate therapy of any dermatitis is required. I believe these patients should be put on anticoagulants for the rest of their lives.

Recently, Dr. Laufman has suggested that the varicose veins of these legs may be an initiating factor in the production of further disease. He has felt that the varicosities result in a periphlebitis which produces more edema and increases the obstruction of the capillary flow, in turn causing anoxemia to the skin with further ulceration. He has felt that the answer is to strip these veins as extensively as possible, and to be sure that the ulcer areas are resected with the plexus of veins found beneath them.

Summary

We have tried to explain some of the pathological physiology in venous thrombosis, with a plea for the use of prophylactic anticoagulants and the use of therapy based on physiologic principles.

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HYDATID DISEASE

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Hydatid disease is produced by the Taenia echinococcus granulosus worm, the smallest of the cestode group. The importance of hydatid disease and its occurrence in man, cattle and other animals has been known for centuries. In some passages of the Talmud reference is made to "clear, limpid, water-filled blebs" of the lung. Even in the time of Hippocrates this disease was known: in his Aphorisms he speaks of "livers full of water." In the years 1781 and 1782, Goeze recognized under the microscope the granulations on the inner surface of the cyst, and thought them to be the heads of small taenia, each with a halo of hooklets. However, it was left to Von Siebold to discover that the parasite was the Taenia echinococcus and that the adult worm developed in dogs which were fed infected livers.

Epidemiology

Hydatid cyst disease is widespread in its distribution. It occurs mostly in sheep-raising countries like Australia, New Zealand, Uruguay and Argentina. Numerous cases are also recorded from southern Europe, Switzerland, Germany, Austria and Siberia. The countries that border the Mediterranean Sea and far eastern countries like China, Japan and the Philippines are not exempt from it. Very

rarely, cases are seen in the United States; these people in all probability had the cysts before their immigration to the United States from the above-mentioned countries.

The Parasite and Its Life Cycle

A definitive host, such as the dog or other carnivora, is infected by ingesting scolices with the flesh or viscera of an intermediate host, such as sheep, hogs, and cattle. The intermediate host acquired the infection by swallowing grass or water contaminated with ova that were passed with the dog's excreta. A man who is an intermediate host may acquire the infection by eating vegetables contaminated by ova; more frequently these are conveyed to the mouth by the hand that has had intimate contact with dogs, especially in the case of children. In the intermediate host, the cestode lives in the tissues and organs, forming cysts filled with a clear fluid. In the definitive host, the parasite lodges in the gastrointestinal lumen.

The Taenia echinococcus measures 3 to 6 mm. in length. It is composed of three segments, plus a little end which is the head of the parasite. The general shape of the parasite under the microscope resembles a shoehorn. The smallest part is the head, having at its vertex a rostellum surrounded by a halo of hooklets, about 35 in number. Behind these hooklets are four suckers by which the

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parasite attaches itself to the mucosa of the small intestine in the body of its victim. Following the head segment there are three proglottids, differing in size. The terminal proglottid, the bulkiest, contains the ova. The ova are very small, measuring about 35 mu in their transverse diameter. Experiments have shown that they are resistant to even extreme cold and can survive for months in freezing water and cold temperature.

Route of Infection

When the liberated ova are swallowed by the intermediate host, the oncosphere, or hexacanth embryo, is hatched in the duodenum. The larvae enter the duodenal wall and, from there on via blood vessels, reach the liver. Some of the larvae escape the sieve of the liver capillaries, reach the pulmonary circulation, and are caught in the capillary system of the lungs, or are dispersed throughout the body.

Once they are caught in an organ, the embryos transform into a very small cyst containing a minimal amount of colorless fluid. This stage is the start of the so-called hydatid cyst. As the cyst grows in size, a differentiation of layers becomes apparent. The parasite itself has an outer laminated ectocyst layer and an inner germinative endocyst layer. The ectocyst is laminated, soft and elastic, and resembles the white of a hard boiled egg. It has a thickness of 2 to 3 mm. and consists, microscopically, of a very thin, hyaline layer without nuclei. The endocyst layer has a granular surface, measures 10 to 25 mu in thickness, and has irregularly arranged cells in single or double rows. It is from the endocyst that brood capsules, and later scolices, are formed. A limpid hydatid fluid is also produced by this layer. A third layer, the pericyst, does not belong to the parasite itself; it is the reaction of the host towards the parasite.

Cyst Development

The cyst grows very slowly. It takes about seven days after implantation to form a miniature cyst. In the second week it measures about 150 mu. In the third month after its implantation the transverse diameter is about 2 mm. As time goes on, the implanted cyst grows

— Rostellum

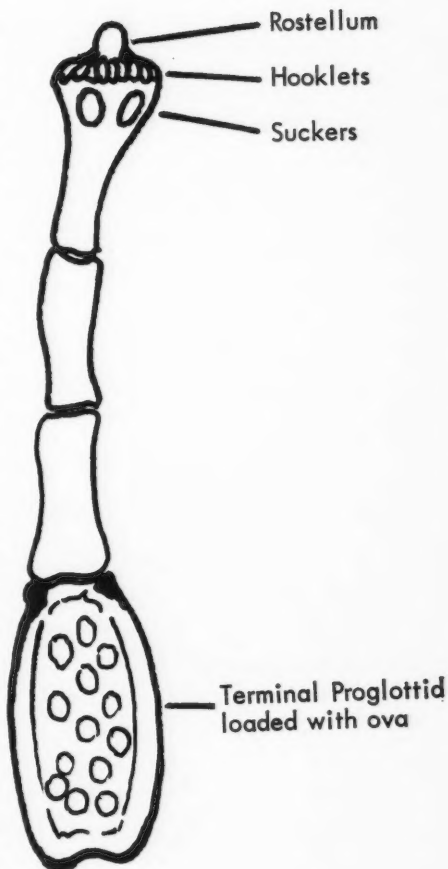— Hooklets

— Suckers

— Terminal Proglottid loaded with ova

Fig. 1

A sketch of the adult Taenia echinococcus granulosus. The actual size is 3-6 mm. and its color is grey. It might be attached to the mucosa of the upper gastrointestinal tract by its four suckers. Its propulsion in the gastrointestinal lumen is by a gentle or rapid undulation of the body. The mature parasite lives 4-5 months in the definitive host's intestinal lumen. During this time the terminal segment liberates the ova of Taenia echinococcus granulosus. These ova, swallowed by the intermediate host, will produce the Hydatid Cyst.

larger and the germinal layer produces brood capsules in which the scolices are formed. These are the heads of the worm without the body. The scolices in the hydatid fluid stay at the bottom of the cyst and are known as "hydatid sand." If they are spilled into the tissues of the host, they produce secondary implantation cysts. On the other hand, these same scolices will mature into flat Taeniae echinococcus in the intestine of a dog or other definitive host which has eaten an infected piece of sheep, cattle, or hog meat.

When the cyst matures, small daughter cysts also gradually grow from the germinal layer, or endocyst, and drop off into the hydatid fluid. In hydatid cysts of the liver, numerous daughter cysts are frequently found in the primary large cysts. In brain hydatids, daughter cysts are rarely found. This has been attributed to the lack of trauma from the outside on these hydatid cysts. The daughter cysts are also composed of an inner germinative membrane and an outer laminated layer. They may occasionally produce
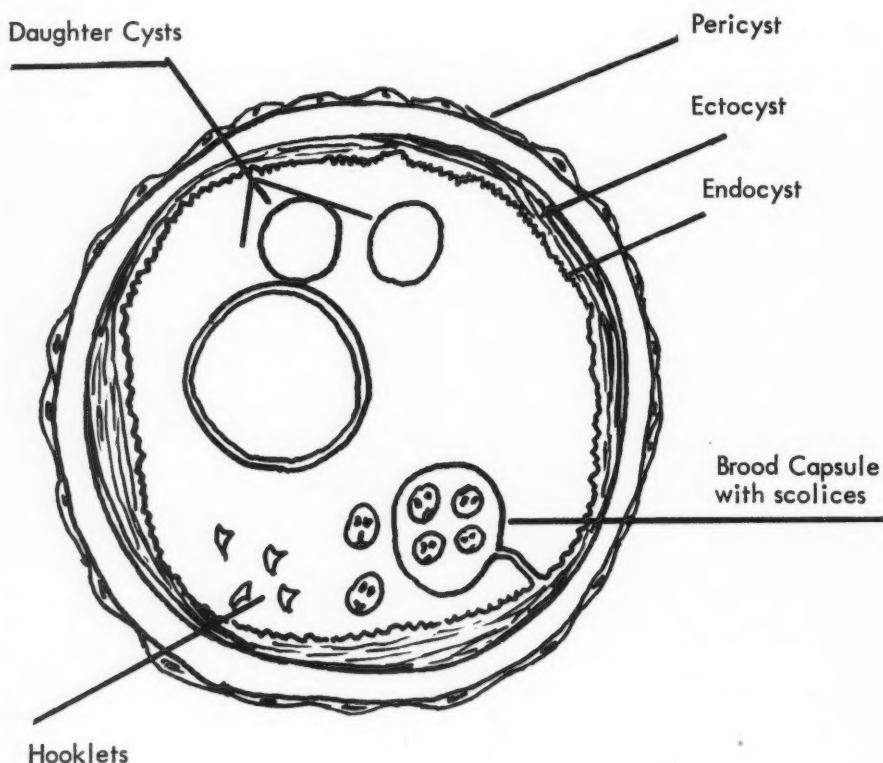

Fig. 2: Diagrammatic sketch of the Hydatid Cyst of the intermediate host.

brood capsules, and rarely a granddaughter cyst may start from this germinal layer.

The clear hydatid fluid that collects within these cysts serves for the nutrition and the mechanical protection of the scolices. Some of the cysts contain large amounts of fluid, measuring 10 to 11 liters. Specific gravity of the fluid ranges around 1.005 to 1.010. It includes approximately 0.5% sodium chloride, 0.35% urea, 0.08% albumin, 0.25% glucose, and 0.09% creatinine, along with traces of proteolytic and glycolytic ferments. Scolices and hooklets of hydatid cysts float in it.

Pathogenesis and Pathologic Anatomy

The oncosphere, or hexacanth embryo, on reaching an organ such as the liver, is caught in the small sieve of capillaries. A cellular reaction is formed around the parasite. It is composed mainly of an infiltrate of eosinophils and a few giant cells. Occasionally, a focal area of hemorrhage occurs and the reaction in the tissue may be so severe as to destroy the implanted embryo. If the embryo survives, a peripheral zone of fibrosis is formed after several months: this is the pericyst encasing the growing cyst.

There are three forms of hydatid cysts. The classical type is found in the liver, where an endocyst, ectocyst, and pericyst are formed. The bone hydatid cyst is a second variety, structurally different from the one in the liver: it has no pericyst, the layers of the cyst itself permeate between the bony trabeculae, and the bone undergoes pressure atrophy, becoming ultimately soft and necrotic. The third type of hydatid cyst is the alveolar form which is mostly seen in southern Germany, Switzerland, and some parts of Russia. This variety produces a spongy mass in the liver consisting of an atypical growth of embryonic tissue without the formation of the laminated ectocyst or the pericyst reaction of the host.

About 65% of hydatid cysts develop in the liver, 15 to 20% in the lung, and the remainder are fairly equally distributed in the other viscera and tissues. (Table I.)

TABLE I.

DISTRIBUTION OF HYDATID CYSTS IN THE HUMAN BODY

210 cases, American University of Beirut, Lebanon, 1935-1955.

Location	Number of Cases
Liver	130
Lung	55
Brain	3
Orbital Cavity	4
Pleural Cavity	1
Abdominal Cavity	1
Bones	2
Kidney	5
Spleen	7
Thigh	1
Pericardium	1

Note: Of all hydatid cysts of the liver, only 5.4% of cases show cysts in the lung as well. However, of cases with cysts of the lungs, only 12.5% show involvement of the liver as well. Of 25 cases of hydatid cyst elsewhere in the body, only 2 (8%) showed involvement of both liver and lungs.

In more than 200 reported cases of hydatid disease in the American University of Beirut, we have noted that about 65% of hydatid cysts are found in the liver, either in single or multiple cyst form. The cysts in the liver have measured from 1 cm. to 30 cm. in diameter. Most of the cysts are found in the right lobe of the liver, probably because the parenchymatous tissue in the right lobe is more abundant than that in the left lobe. Usually the number of hydatid cysts in the liver is few, but I have seen the case of a small child, who, after swallowing the feces of the pet dog in the house, developed within six months a hepatomegaly which on exploration showed a granularity simulating that of a postnecrotic liver cirrhosis. At biopsy these nodularities proved to be hydatid cysts. In this case, there were innumerable cysts in the liver.

The number of hydatid cysts in the lung comprises about 25% of the total number of hydatids in our series. The lungs are affected in the same way as the liver; however, the right lung carries a slightly higher percentage of cases, probably due again to the increase in parenchymatous tissue in the right side. The cysts may be single or multiple, unilateral or bilateral. A characteristic of the lung hydatid is the complete absence of daughter cysts inside the main primary cyst. Another characteristic is the usual presence of a communicating segment bronchiole between the pericyst and ectocyst. The rest of hydatid cysts, comprising about 10%, are distributed throughout the body, in such areas as the orbital cavity, the spleen, the brain, the spinal column, and, finally, the femur and soft tissues of the thigh, the abdominal cavity and the pericardium.

Diagnosis

In the history of the patient, the identification of the country of origin and the country where the patient had lived as a child is of some importance. A history of a pet dog in the house carries some weight, too. In the adult, the passage of grape-like cysts in the urine suggests a hydatid cyst of the kidney, (Fig. 3). The coughing up of the membrane is diagnostic of a ruptured cyst of the lung. A differential count of the blood with an uncomplicated hydatid cyst shows an eosinophilia which ranges from 5 to 10%. X-ray studies are especially helpful in the diagnosis of the lung hydatid cyst. A translucent halo between the round lung shadow and the pericyst is diagnostic. The "water lily" sign is suggestive of a ruptured hydatid cyst with the cyst membrane floating on the fluid surface.

In the X-ray diagnosis of the hydatid cyst of the liver, the only suggestive finding is the shadow of a calcified capsule, suggestive of a cyst in the liver. Skin tests, commonly known as Casoni's test, are of great value. In this test about 90% of patients with live hydatid cysts will show a positive skin reaction, with very few false positives. A Weinberg complement-fixation test is of value also. Dr. A. Garabedian, of the American University of Beirut, recently developed a hemag-glutination test in hydatid disease of man. So far, the results have been very encouraging in the diagnosis of this disease.

Complications

The most important complication of hydatid disease is the rupture of the cyst. This occasionally produces an anaphylactic reaction characterized by high fever, dyspnea, vomiting, delirium, syncope and death. (This complication at the time of operative removal can be halted by immediate anti-anaphylactic therapy.) Fortunately, this happening is rather rare, but when it occurs it can be fatal.

The most common complication is secondary infection of the hydatid cyst. When a hydatid cyst in the liver becomes secondarily infected, the germinal layer degenerates into a mushy, soft, filamentous membrane; the bile leaks into the cyst, and the fluid is greenish in color. As time goes on, the laminated layer becomes calcified. Calcification seen in the wall of a hydatid implies that the cyst is non-viable and dead.

Another complication of importance is the rupture of a cyst into a duct, such as a major biliary canal, producing an obstructive, infectious hepatitis. In our series of over 200 cases we have had three such cases. Another instance of rupture occurs in cases of hydatid of the kidney where the cyst opens into the pelvis of the kidney, the patient eliminating small water-filled cysts or membranes in the urine. A rare complication is the opening of a cyst into a major bronchus of the lung. The patient may cough out the whole ectocyst of the parasite. Rupture into the general peritoneal cavity is an undesirable complication predisposing to a luxuriant growth of multiple cysts. The rupture of a hydatid cyst into the pleural cavity has a similar course. Implantation hydatid in operative wounds has been seen only four times in our series. Occasionally, a bone which is infected by this parasite develops a pathological fracture.

Since a cyst is a space-occupying lesion, it will produce a hydrocephalus when localized in a strategic position in the brain. We have had one case where the transverse diameter of the cyst was 15

Fig. 3: Hydatid cyst of the kidney with a urate stone in the renal pelvis.
The pre-operative diagnosis was a nonfunctioning kidney with an impacted stone in the pelvis and a resultant moderate hydronephrosis. At operation, the impacted stone was found to be associated with a large hydatid cyst in the upper pole of the kidney. The lower pole renal parenchyma was found to be inadequate for a plastic repair, and a nephrectomy was performed. The post-operative course was uneventful, and, at three year followup, there was no recurrence.

cm. and the child had only a rim of compressed brain tissue around the cyst. The hydatid cysts in the orbit will produce a unilateral exophthalmus on that side. A spinal column hydatid cyst occasionally may compress the spinal cord, producing a paraplegia, (Table II).

Table II

COMPLICATIONS OF HYDATID CYSTS

210 cases, American University of Beirut, Lebanon, 1935-1955

Complications	Number of Cases
Infected, preoperative	25
Rupture into the biliary tree	3
Rupture into a bronchus	1
Rupture into renal pelvis	1
Rupture into pleural cavity	2
Rupture into peritoneal cavity	1
Incision (scar) implantation	4
Anaphylactic shock	2
Milder anaphylactic states	9
Exophthalmus	4
Increased intracranial pressure	3
Paraplegia	1

Treatment

Hydatid cysts of the liver and lungs showing calcification on x-ray examination are presumed to be inactive and dead; if they are asymptomatic, these space-occupying lesions could be left alone. Hydatid cysts of the liver can be treated in one of several ways. We have had an occasional cyst high up in the dome of the liver, rather small in size, which was aspirated and the cavity irrigated with 70% alcohol, or 4% formaldehyde, producing a coagulative necrosis of the germinal layer. However, such cases treated by us were too few in number to allow a definite conclusion on the effectiveness of this treatment. A large majority of our cases have been treated by two-stage intervention therapy: first, the marsupialization of the cyst surface; and second, the aspiration and drainage of its contents 7 or 10 days later. This is a sure way of a definitive cure of the hydatid cyst. We also think that infected cysts in the liver should be treated by marsupialization and drainage. However, one disadvantage to this treatment is the long morbidity following the drainage of the cyst cavity.

The dangers of secondary hydatid cysts at the site of marsupialization are minimal and we have had only four cases in our series of over 200 cases in the American University of Beirut. Probably the resistance of the granulating surface of the wound serves as a protection against the implantation of the scolices at the site of the incision.

Another technique which we have adopted of late has been a one-stage operative removal of the cyst. Caution is necessary not to spill any of the hydatid fluid into the freshly cut tissues. The surface of the wound is well protected by pads. The cyst is aspirated as much as possible by a large trocar with a strong suction attached to it. Then the cavity is thoroughly and repeatedly irrigated and aspirated, the surgeon seeing to it that no remnants of the cyst wall or daughter cysts are left in the cavity. After this assurance, the surgeon has to obliterate the cavity by putting interrupted catgut sutures in the pericyst, to eliminate a residual cavity in the liver. After these procedures are completed, the opening in the cyst wall is closed. The peritoneum is closed without drainage.

So far, in our series of about 20 cases, we have had no complications resulting from this form of therapy. Occasionally, the cavity in the liver is filled with hypertonic sodium chloride solution and the cyst wall closed without an attempt to obliterate the lumen of the cavity. The omentum could be tucked into the cavity as an alternative to the above techniques.

Hydatid Cyst of the Lung

There are also several ways of treating hydatid cysts of the lung. These cysts are most often rather small and uncomplicated, and are usually amenable to removal, with obliteration of the space by interrupted sutures. Attention must be

paid to maintaining the patency of the communicating segment bronchiole between the pericyst and the laminated ectocyst to avoid a segmental atelectasia. The complicated hydatid cysts of the lung, which are usually fairly large in size, can be treated by lobectomy. Under no circumstances is a blind needle aspiration of the hydatid cyst permissible.

Hydatid Cyst of the Brain and Bone

These cysts usually occur in the younger age group, and they have been a rather disappointing problem to us. The high rate of local recurrence in the brain has been a constant danger. The same might be said about the hydatid cyst of the bone where the pericyst, or host reaction around the cyst, is totally absent. The cyst cavity has to be curetted off, predisposing to implantation in the freshly cut tissues.

Problems in Hydatid Disease

The route of infestation of man as described in textbooks is through the portal-vascular system, with stoppage of the hexacanth embryo in the liver. Some of the embryos escape into the pulmonary circulation with stoppage in the pulmonary parenchyma. Some may then escape from the pulmonary capillary tree into the systemic circulation with implantation in other body tissues. The fact that the pulmonary hydatid cyst does not have an associated hydatid cyst or cysts in the liver is surprising. Also, hydatid cysts which are dispersed in the structures of the body, such as the thigh, do not have associated hydatid cysts of the lung and liver. One explanation of this

paradox could be that the entry of the hexacanth embryo into the tissues of the intermediate host is not only through the blood capillaries in the intestinal villi, but through the lacteals as well, short circuiting the portal circulation and entering directly into the pulmonary and systemic circulations.

We have no drug therapy to stop the growth of these cysts. Radiation therapy has been disappointing. Inducing an immunity in the children of the countries affected by this disease would be the ideal solution to the problem.

The problem of secondary implantation hydatid cysts at an operative site is taken care of only by a scrupulously careful operating technique. This is of great importance in hydatid cysts of the brain when, almost as a rule, after several months or a year there is a recurrence of the symptoms of a space-occupying lesion. We have no medical therapy to prevent these secondary implantations.

In spite of the help offered by x-ray and laboratory procedures in the diagnosis of this disease, there is a small percentage of 10 to 15% where diagnostic means have failed. More delicate tests, with a higher index of accuracy, are certainly needed in the diagnosis of hydatid disease in man.

Acknowledgement

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RECOGNITION OF RENAL DISEASE IN CHILDREN*

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Modern medicine has emphasized the importance of early recognition of renal disorders in all age groups. We are rapidly approaching the era when early detection and institution of specific therapy will result in a cure of disorders which formerly progressed, slowly or quickly, ultimately to renal failure and death.

The Nephritides

Acute glomerular nephritis and the nephrotic syndrome are probably the most common disorders of the kidney encountered in childhood. It is probably well known that **acute glomerular nephritis** occurs with equal frequency in each sex, and the age group usually affected is covered in the all encompassing elementary school age. (Table 1) Following an upper respiratory infection by one or two weeks, the disease is usually ushered in by edema, hematuria, or both. Examination of the urine usually reveals a mild proteinuria, with a moderate to severe degree of hematuria. The sedimentation rate is elevated. The BUN may or may not be elevated. Since most cases, but not all, are immunologically associated with certain types of group A beta hemolytic Streptococci, the serum may reveal a high titer of streptococcal antibodies. In some instances the provoking Streptococcus may be cultured and typed.

As in acute glomerular nephritis, the **nephrotic syndrome** also has no predilection for any sex. Most cases, however, are discovered before school age. This disorder also is frequently preceded by an upper respiratory infection. The presenting complaint is usually facial or generalized edema. (Table 1) Examination of the urine reveals massive proteinuria and careful examination of the sediment will reveal desquamated tubular cells undergoing fatty degeneration, the so-called "oval fat bodies." The sedimentation rate is accelerated. A study of the serum will reveal a marked depression of the total protein which, on paper electrophoresis, will demonstrate a depression of the albumin, a slight rise in the alpha-2 and beta globulin, and a marked depression of the gamma globulin fractions. Usually, significant titers of streptococcal antibodies are not demonstrated. Recently, Heymann[1] reported four cases of children with the nephrotic syndrome, but in addition they manifested hematuria, hypertension, and an elevation of streptococcal antibodies. He called this the nephrotic stage or phase of acute glomerular nephritis. We too have encountered similar patients and we don't know why their illness could not have just as well been called the nephritic phase or stage of the nephrotic syndrome.

TABLE 1

The Nephrides

	Sex	Age	Manifestations	Urine	Serum	Blood Pressure	I.V.P.
Acute Glomerular Nephritis	M = F	> 5 yrs.	Edema Hematuria Both	Mild Proteinuria Loaded with RBCs RBC casts	Elevated A.S.O. titer	Normal or Elevated	Normal
Nephrotic Syndrome	M = F	< 5 yrs.	Edema	Massive Proteinuria Occasional RBC Oval fat bodies	Hypoproteinemia Hypoalbuminemia Hypercholesterolemia	Normal	Large Kidneys
Chronic Glomerular Nephritis	M = F	Children Adolescents	Failure to thrive Anemia Bleeding	Moderate Albuminuria Fixed Specific Gravity Casts Few RBCs	Azotemia	Elevated	Small Contracted Kidneys

Subacute or **chronic glomerular nephritis** occurs frequently enough to describe their usual mode of onset. These disorders are rarely preceded, both in children and adults, by a bona fide, well documented attack of acute glomerular nephritis which then goes on, slowly but surely, to develop chronic glomerular nephritis as we know it. Usually, children with these disorders are brought to the physician because of failure to thrive, severe anemia, loss of weight or proneness to infection. (Table 1) Headache and vomiting are common. Bleeding is not unusual. Edema and urinary symptoms are conspicuously absent. Physical examination may reveal hypertension, anemia, and hemorrhages or exudates in the retina. Laboratory studies will often reveal poor kidney function with low, fixed specific gravity. Inulin, creatinine, and para-amino-hippurate clearance studies are usually impaired. A persistent azotemia, acidosis, hyperkalemia, and hyperphosphatemia are common. Intravenous pyelograms are usually not too helpful, but may demonstrate small contracted kidneys.

Unilateral Renal Disorders

The following renal disorders are encountered less frequently. Since prompt therapeutic measures, however, may result in a cure, early recognition is mandatory.

Renal vein thrombosis occurs more frequently than one expects. It usually affects young infants. Kauffman,[2] reviewing the world literature, notes that 60 per cent occur in the neonatal period. Abeshouse,[3] in 1945, reported 228 cases; 112 occurred in children under 2 years of age, and 90 of these children were less than 2 months of age. Zuelzer,[4] in 1951, reported 12 cases; all but one were under 6 months of age. Unilateral renal vein thrombosis occurs with equal frequency in both sexes, but unilateral involvement in females occurs more frequently on the left side. It is usually associated with infections, diarrhea, and dehydration. (Table 2) Renal vein thrombosis results in hemorrhagic destruction of the renal parenchyma with subsequent loss of function. Thus, the presence or sudden onset

of hematuria and a mass in the region of the kidneys in a child with infection, diarrhea, and dehydration should alert one to this diagnosis. Frequently, other veins are thrombosed: the usual sites are the cranial sinuses and the tributaries of the portal system; therefore, symptoms related to these organs may also be present.

The observations of Zuelzer, Morrison,[5] and others suggest that in infancy the thrombosis either is primary, in the small radicles with extension secondarily into the main branches of the renal veins, or occurs simultaneously in branches of small and larger caliber. Very little evidence exists to suggest that retrograde extension of thrombosis from the main stem of the renal vein occurs. Campbell[6] suggests that overwhelming sepsis and toxemia consequent to the major initial condition, whether it be ileocolitis or peripheral infection, with pain in the loin accompanied by hematuria, tenderness, and sudden renal enlargement, suggest the diagnosis of renal vein thrombosis. He also recommends that ureteral catheterization may reveal the affected side when this is in doubt. There is some evidence that the envelope of pathogenic **E. coli** damages the endothelium of veins; however, morphological evidence of inflammatory changes or necrosis of the veins is usually absent. Whether a systemic factor due to hemoconcentration, slowing of the blood stream, or damage of the endothelium is a cause of renal vein thrombosis is at present not known.

Unilateral renal disease with hypertension should be suspected in all cases of hypertension in childhood. (Table 2) The usual manifestations are those due to hypertension, i.e., headache, vomiting, eye signs, etc. The usual laboratory tests are normal. The recognition of unilateral renal disease requires the radiological demonstration of the affected kidney with the use of contrast material by an intravenous pyelogram, retrograde pyelogram, or abdominal aortogram, in that order. If visual demonstration fails, the ureters are catheterized and function studies attempted. Quantity of urine and salt are determined; excretion of dye, creatinine, and urea are all measured bilaterally.

TABLE 2

Unilateral and Bilateral Renal Disorders

	Sex	Age	Manifestations	Urine	Serum	Blood Pressure	I.V.P.
Renal Vein Thrombosis	M = F	<1 yr.	Sepsis Hematuria Mass in region of kidney	Massive Hematuria	Normal or Azotemia	Normal or Elevated	No Visualization on Affected Side
Unilateral Renal Disease with Hypertension	M = F	Children Adolescents	Headache Vomiting Eye Signs	Normal	Normal	Elevated	Normal or Impaired Filling on Affected Side
Wilms' Tumor	M = F	<3 yrs.	Swelling of Abdomen Mass in Abdomen Abdominal Pain	Normal	Normal	Normal	Marked Distortion of Kidney. (No Displacement)
Hydronephrosis (Pure)	M = F	Early Childhood	Failure to thrive Polyuria Frequency Loin Pain	Alkaline Low specific gravity No response to pitressin	Normal	Normal	Dilated Pelvis and Calyces
Polycystic Kidneys	M = F	Early Childhood	Failure to thrive Mass in Abdomen Other Congenital Anomalies	Normal	Normal or Azotemia	Normal or Elevated	Elongation of Pelvis (Spider Calyces)
Chronic Pyelonephritis	F > M	Early Childhood	Failure to thrive Dysuria Polyuria Loin Pain	WBC with Clumps Trace Albumin	Normal or Azotemia	Normal	Normal or Small Kidneys

Finally, if these studies do not demonstrate the involved kidney, then I[131]-Diodrast is injected and the amount of tagged material is counted over both kidney areas. Kincaid-Smith[7] and others have emphasized that most cases of unilateral kidney disease with hypertension are due to chronic pyelonephritis. When this diagnosis is made, the question of nephrectomy must be decided. It should be remembered that approximately only one-third of these cases will benefit by nephrectomy.[8]

Wilms' tumor, embryonal nephroma, or nephroblastoma was first described by Rance in 1814. Up to 1899, the theory of the origin of this tumor was variable indeed. At that time, Wilms suggested that the tumor originated from undifferentiated mesoderm, and this theory is generally accepted today. The diagnosis is usually suspected by the following signs and symptoms: 1) an abdominal mass, usually discovered by the mother or the physician; 2) fever and abdominal pain; 3) hematuria, uncommonly; and 4) hypertension, which is presumably caused by perirenal inflammation with renal ischemia. This tumor occurs with equal frequency in both sexes, usually in early life. (Table 2) Caffey[9] has pointed out that the intravenous pyelogram will reveal marked distortion of the calyces with very little displacement, while other abdominal masses will result in very little distortion but marked displacement of the kidney. Invasion of the renal vein occurs frequently; thus, metastases to the lung are common.

Bilateral Renal Disorders

Hydronephrosis is usually secondary to a urinary tract obstruction and in many instances leads to infection with subsequent development of pyelonephritis. Which plays a more important role in the clinical picture, the obstruction and hydronephrosis, or the infection, is a moot question and the answer is that both probably play a significant role. Congenital urinary tract obstruction with its subsequent aftermath is one of the more common causes of failure to thrive. Polyuria, frequency, urgency, enuresis, and pain over the bladder or pain with urination should lead one to suspect this underlying disorder. (Table 2) Examination of the urine may demonstrate pyuria. It should be noted, however, that pure hydronephrosis without superimposed infection can lead to a pitressin-resistant-polyuria with excretion of a hypotonic alkaline urine. This observation, together with experimental work, suggests that obstruction somehow functionally impairs that portion of the nephron dealing with concentration and acidification of the urine. The intravenous pyelogram will usually demonstrate the dilated calyces and ureters and, frequently, the cause of the obstruction. An ordinary and a voiding cystogram may demonstrate the obstruction in the bladder or urethra. Finally, cystoscopy and retrograde studies of the ureters may be necessary to demonstrate the congenital malformation.

Polycystic disease of the kidneys is almost always bilateral; however, one of the kidneys may be so minimally involved as to appear grossly normal. The signs and symptoms, and thus the age when the disease becomes manifest, will depend on the degree of parenchymal involvement. Usually, the manifestations of this disorder are failure to thrive, a large, protuberant abdomen, palpable masses in the flanks, and other congenital anomalies, such as polydactylism, hydrocephalus, or cardiac anomalies. (Table 2) Azotemia and hypertension may be present. Tubular cysts in children do not communicate with the renal pelvis; glomerular cysts in both children and adults also do not communicate with the renal pelvis; therefore, one can easily visualize why the pyelograms reveal flattening and elongation of the pelvis and the calyces, respectively.

Chronic pyelonephritis was alluded to before in the discussion of hydronephrosis and unilateral renal disease with hypertension. Because of a shorter urethra, which is more easily contaminated, females are more often afflicted with this disease than males. Many of these infections ascend to the kidney via the bladder and ureters. This disorder is directly associated with congenital obstructive uropathies. The symptoms are

TABLE 3

Renal Tubular Disorders

	Sex	Age	Manifestations	Urine	Serum	Blood Pressure	I.V.P.
1. Vit. D Resistant Rickets	M > F	Early Childhood	Failure to thrive Rickets Anemia	Glycosuria No Aminoaciduria	Low Phosphorus Normal or low Calcium Elevated Alkaline Phosphatase	Normal	Normal
2. Cystinosis	M = F	Early Childhood	Failure to thrive Rickets Anemia Conjunctivitis	Glycosuria Aminoaciduria Albuminuria	Low Phosphorus Normal or low Calcium Elevated Alkaline Phosphatase	Normal	Normal
3. Nephrogenic Diabetes Insipidus	M = F	Early Childhood	Failure to thrive Polyuria Polydipsia Dehydration Fever of Undetermined Origin	Low specific gravity No response to Pitressin	Hypernatremia Azotemia	Normal	Normal

usually those of fever, frequency, nocturia, polyuria, dysuria, and pain over the bladder or flanks. (Table 2) The urine will contain pus, bacteria, and some albumin. Azotemia usually occurs late in the disease. The infection usually spreads into the renal parenchyma and, as it does, fibrosis of the interstitial tissue produces ischemia and thus early hypertension. Since urine cultures are so easily contaminated, and since catheterization is not generally acceptable, we have been paying more attention to the bacterial colony counts of a clean voiding specimen. Colony counts of over 10,000 per milliliter of urine are significant of urinary tract infection.

Renal Tubular Disorders

Finally, the renal tubular disorders should be discussed. We will only consider the following:

Vitamin D resistant rickets is an inborn error of metabolism in which there is a high renal clearance and poor tubular reabsorption of phosphorus. This results in the usual signs of rickets. It has been found in several members of a family, but the genetic mechanism is variable. Winters[10] has demonstrated that this disorder is transmitted in most instances as a sex-linked dominant trait. Hemizygote males manifest a much more serious disorder than the heterozygote female, who usually only demonstrates a hypophosphatemia. Why this should be is not settled, but it is interesting to speculate that the normal X chromosome from a normal female in some way interferes with the expression of the involved X chromosome from the male. A sporadic form of this disease, which cannot be distinguished from the sex-linked form, has been described. Since the sex-linked form of the disease is more common and severe in males, and since the sporadic form occurs with equal frequency in both sexes, this disease should be encountered more frequently in males. However, if hypophosphatemia alone or in combination with bone defects is looked for, the disease becomes equal in both sexes. The usual presenting complaints are dwarfing, rickets, failure to thrive, and anemia, in spite of adequate intakes of vitamin D. (Table 3) Examination of the serum reveals a hypophosphatemia with a normal or low calcium. The alkaline phosphatase is elevated. The urine will contain increased quantities of calcium and phosphorus, but no glycosuria or aminoaciduria.

Cystinosis and the **Fanconi syndrome** are not one and the same disease. The Fanconi syndrome with cystine storage in various organs is cystinosis. However, many cases of the Fanconi syndrome have been shown to lack cystine deposits on post-mortem examination. The usual clinical manifestations are stunting of growth and resistant rickets. (Table 3) Examination of the urine reveals an aminoaciduria, glycosuria, albuminuria, organic aciduria, and phosphaturia, which suggests that there is a tubular deficiency in reabsorption of phosphorus, amino acids and glucose, and in the mechanism for reabsorbing base without acid. The serum will usually demonstrate a hypophosphatemia, hyperchloremic acidosis, elevated alkaline phosphatase, and normal values for sugar and alpha-amino nitrogen, all of which points out that the disturbance is one of tubular reabsorption. Progressive renal failure usually ensues with azotemia and hyperkalemia. Whether this progressive renal failure is due to the toxicity of cystine or to a generalized disturbance of amino acid metabolism is at present not known. In cystinosis with cystine storage, slit lamp examination of the cornea or examination of the bone marrow will demonstrate cystine crystals.

Nephrogenic diabetes insipidus is also an inborn error of metabolism. It is transmitted as a sex-linked recessive or as an autosomal dominant gene. If the disease is seen in the former mode of transmission, it will manifest itself in males only. If the disease is determined to be the latter form, it will be observed equally in both sexes. As the name implies, it is a disorder characterized by diabetes insipidus, but not due to a deficiency of antidiuretic hormone; rather, the renal tubular cells merely do not respond to antidiuretic hormone. It is characterized by bouts of fever of unknown etiology, together with dehydration which responds poorly to fluid and electrolyte

therapy. There is a history of tremendous water intake, together with polyuria. The urine is pale and the specific gravity is rarely above 1.010; the serum usually reveals a hypernatremia. Failure to thrive and mental retardation are common. (Table 3)

Summary

In summary, several of the more common and rare renal disorders encountered in children have been described. The age, sex predilection, clinical manifestations, laboratory aids, and genetic mechanisms were briefly discussed.

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INTERSTITIAL CELL TUMORS OF THE TESTIS*

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Spontaneous development of interstitial, or Leydig cell tumors of the testis is a relatively rare occurrence in most mammals.[1] The incidence of spontaneous interstitial cell tumors in dogs[2,3] is over 50%, which is higher than that in any other species. In dogs over 12 years old the incidence may be as high as 80%.[4] Spontaneous interstitial cell tumors have been reported in the horse[5,6] and in the mouse.[7,8,9] In 9,500 autopsies of non-inbred male mice, tumors were found in 28 mice ranging from 9 to 34 months of age.[10] Strain H mice appear to have a particularly high incidence of spontaneous interstitial cell tumors, ranging from 38 to 100%, the incidence being higher in older animals.[11,12] In a combined review of over 10⌐0 human testicular tumor cases, Friedman and Moore[13] and Dixon and Moore[14] found that less than 1% were interstitial cell tumors, and these were usually benign. Their morphology does not differ essentially from those occurring in dog or mouse.[15–18]

Experimental Induction

It had been shown that with the administration of estrogen to stock mice[19,20] and strain A mice[21,22] there developed a hypertrophy and hyperplasia of interstitial cells of the testes. Burrows, in 1937,[23] was the first one to demonstrate that the administration of estrogen to stock mice for 6 to 8 months led to development of an interstitial cell tumor of the testis. Since the seminal vesicles and prostate gland regressed in early stages of the treatment and later enlarged, he concluded that the tumors produced androgen. This has been confirmed by Hooker and Pfeiffer[24] and others. Signs of androgenic activity appear only when the nodule or nodules of interstitial cells have attained significant size.

Interstitial cell tumors developed in testes of infantile rats 8 to 11 months after being transplanted into the spleen of castrated adult rats but not of intact rats.[25,26] Autografting of adult testes to spleens of bilaterally gonadectomized rats was also effective in producing pure Leydig cell tumors.[27] Since the pituitary of castrates is known to have an elevated level of gonadotrophin production, this was considered support for the role of the pituitary in the development of testicular tumors. However, in strain A mice, intra-

splenic transplants of infantile testes into castrated adult mice resulted in testes simulating cryptorchidism, but without neoplastic changes in interstitial tissue.[28]

Attempts to induce interstitial cell tumors in rats by administration of estrogen have been unsuccessful.[29,30] Even strain AxC rats, which develop interstitial cell tumors spontaneously, are resistant to estrogen treatment.[31]

Contrary to earlier reports, induction of these tumors does not appear to be strictly limited to only two strains of mice. Testicular tumors have been induced in JK,[32] white label, and IFS mice[33] with triphenylethylene, which permits a longer period of treatment because of lower toxicity. One tumor has developed in a C3H mouse[32] treated with triphenylethylene.

Gardner[34] also found that if strain A males or females are hybridized with strains not susceptible to interstitial cell tumors, such tumors developed in estrogen-treated hybrids. When tumor-susceptible females of BALB/C (tumor incidence, 80%) were mated with males from resistant or low incidence strains (0-12%), tumor incidence in offspring ranged from 0-67%.[35] None of the F_1 hybrids were as susceptible as BALB/C.

Gardner and Boddaert[36] observed development of testicular tumors in interstitial cell tumor-resistant mice (C_{57} x CBA) treated with tri-p-anisyl chloroethylene (TACE) for over 2 years, but not in animals treated with estradiol esters. In contrast, strain A mice did not develop tumors when treated with TACE.[37] This suggests that some "tumor-resistant" strains may develop tumors if treated for an adequate period with proper estrogen. It may be of some significance that tumor-resistant mice strains RIII, C_2H and CBA are more sensitive than strain A and BA(C) to estrogen based on depletion of testicular interstitial and tubular tissue.[38,39]

Tumor Histology

Upon gross examination, the tumorous testes are gray, yellow, brown or dark red in color. They usually exhibit considerable vascular congestion, especially on the tunica albuginea. In most cases, the surface is smooth, while a few have a distinctly nodular appearance.

After three months of treatment with estrogen in strain A or BA(C) mice there is an increase in the number of interstitial cells, most often showing hypertrophy, usually most conspicuous in the hilar area. This is accompanied by a disorientation and vacuolation of identifiable Leydig cells and the appearance of large brown phagocyte cells. These cells contain ceroid, formed as a polymer of peroxidized and unsaturated fatty acids.[40,41] A similar pigmented cell also forms in the adrenal cortex[42,43] with estrogen administration. The phagocytic nature of the brown cells is shown by their exclusive uptake of India ink particles after injection into testes. The large brown cells may persist for many months. Gardner and Boddaert[36] propose their Leydig cell origin, while Hooker and Pfeiffer[24] designate them as foreign mesenchymal cells.

After the early hypertrophy, the interstitial cells regress. The cells seem to be taken up by the brown cell macrophages. There appear spaces between the tubules which contain only mesenchymal elements, fibroblasts, connective tissue fibers and erythropoietic foci.[36] During hypertrophy and hyperplasia, there is a marked increase in reticular fibers in the intertubular areas. Since the degree of change in interstitial cells is never precisely the same in the entire testes, no testis clearly reveals intertubular spaces throughout. However, there is a definite and constant progression of changes.

After degeneration of hypertrophied cells, small nodules form from primitive mesenchymal cells between spermatic tubules. The nodules proliferate to form solid sheets or cords of large vacuolated, polygonal first-stage cells which contain large, strongly eosinophilic cytoplasmic granules with dark nuclei supported by sparse stroma. Vacuolation of the hypertrophied Leydig cells is thought to be due to their secretory exhaustion. Later, second stage medium-sized cells resembling normal Leydig cells are seen. Finally, third stage small, basophilic, hyperchro-

matic cells containing pyknotic nuclei predominate. Throughout the development of the tumor, the central cells are somewhat smaller than the peripheral cells, which are mixed with brown cells. The growth of the nodule accounts for the increase in the size of the testis.

A similar sequence of events has been shown in spontaneous tumors of old dogs. In mice, metastasis occurs via lymphatic and blood vessels by first stage tumor cells.[24, 44] Andervont et al.[45] have pointed out the great variability in the growth pattern of interstitial cell tumors. There appear to be many general and local factors that influence the progression and fluctuation of this tumor, since it acts like a highly unstable biological system.

Enlargement of hyperplastic interstitial cell areas presses the surrounding seminiferous tubules further and further apart, ultimately to the periphery of the testis. Some tubules show normal spermatogenesis while others are in a state of degeneration or atrophy. The hyperplastic areas contain remnants of spermatic tubules whose walls are reduced to the basement membrane. These tubules contain an eosinophilic staining fluid or are lined by Sertoli cells and spermatogonia. In the non-tumorous portions of the testis, the tubules may have active spermatogenesis. All stages of tubular alteration may occur in the same testis, ranging from tubules reduced to a basement membrane to tubules with normal spermatogenesis. Agglutination of spermatozoa, clumping of spermatids, accumulation of multinuclear cells, and cellular debris intermixed with homogenous eosinophilic droplets in tubules have been observed frequently. Atrophic changes were usually more extreme in tubules adjacent to the tumorous areas. Remnants of spermatic tubules are seen in the tumor and on the periphery.

Mechanism of Experimental Induction

The pituitary glands of estrogen-treated mice, during the first few months of treatment, show a decrease in acidophilic granulated interstitial cell stimulating hormone (ICSH) secretory cells and an apparent increase in chromophobe, non-secretory cells.[31] After about 8 months of treatment, acidophilic cells reappear in normal numbers independent of the appearance of testicular tumors. In castrates, there is a similar but maintained increase in pituitary basophils and, to a lesser extent, of acidophils.

Gardner[22] and Hooker and Pfeiffer[24] postulated that estrogen produced interstitial cell tumors through its stimulatory effect on production and release of ICSH. ICSH acted to stimulate growth of Leydig cells. Most experimental work has revolved around testing the hypothesis of Gardner and of Hooker and Pfeiffer relating development of interstitial cell tumors to production of ICSH.

This hypothesis has not been supported by the results of the administration of a variety of gonadotrophin preparations to mice. Pfeiffer and Hooker[46] found that when pregnant mare serum, which has a high titer of follicle stimulating hormone (FSH) with some ICSH, is administered to mice, the interstitial cells at first showed hypertrophy, followed, in most cases, by a regression, probably due to antibody formation. In a few cases the interstitial cells formed nodules ranging in area from one-third to twice the cross-sectional area of a tubule and were well-localized, especially in the hilus area. In a few other cases, the cells merely showed a persistent generalized hypertrophy. While estrogen produced tumors after 5 to 6 months of treatment, the pregnant mare serum did not produce a distinct tumor, even after 1½ years of treatment. However, the pregnant mare serum did enhance tumor development in mice when administered after termination of or simultaneously with estrogen treatment.[47,3]

Simpson and von Wagenen[48] were only able to produce multiple peritubular nodules in testes of monkeys treated chronically with ICSH. The nodules persisted for several months after treatment was discontinued. These cells, however, did not enlarge to form typical Leydig cells, nor was a Leydig cell tumor formed. The authors suggested that the cells of the nodule had a common origin with

Leydig cells from the peritubular un-differentiated encapsulating cells.

Blivaiss et al[49] found that administration for 6 months of sheep ICSH to strain A mice, starting at 1 month of age, produced only a marked hypertrophy of Leydig cells in 24 out of 27 cases studied, and hyperplastic nodules in 2 others, occupying an area equivalent to 2 or 3 tubules. Long term treatment with these materials is complicated by the antigenic properties of these preparations, so the response may be reduced.

The possible role of pituitary gonado-trophin in induction of interstitial cell tumors is supported by studies with anti-gonadotrophic serum. Ely[50] reduced the size of the tumorous area in estrogen treated strain A mice by the simultaneous administration of anti-gonadotrophic serum produced in response to a crude sheep pituitary extract. After administration to estrogen-treated strain A mice of an anti-ICSH serum, produced in response to a highly purified ICSH, Blivaiss et al[51] found a retardation in development of tumorous testes both in terms of weight and histology. They also observed a reduction in weight of seminal vesicle which suggested a decrease in hormone secretion.

In assay of pituitary glands from estrogen-treated mice in hypophysectomized animals, Gardner[39] failed to reveal detectable amounts of gonadotrophin or differences between strains susceptible or resistant to tumor formation. Blivaiss et al[52,53] found that ICSH content of pituitaries from strain A mice treated with estradiol benzoate for 2-12 months, when assayed in immature male mice, was over 40% less than in controls of the same age. With increasing age, the differences between the two groups decreased. The period of decreasing difference in pituitary ICSH corresponded to the time of tumor development. In a similar procedure with a tumor resistant strain, $C_{57}BBF_1$, pituitary ICSH content of estrogen treated mice was 25% of controls of similar age with little decrease in differences between the two groups with increasing age.[53] This difference between sensitive and resistant strains in re-sponse of pituitary ICSH to estrogen treatment may be a factor in tumor development.

To determine the role of pituitary secretions in tumor induction, Trentin[54] studied the effect of transplantation of mouse testes from susceptible and non-susceptible strains to their F_1 hybrid. He found that a tumor developed to a significantly greater degree during estrogen administration if transplanted testes were taken from parent susceptible strains. In testes from resistant donors, only one tumor and one nodule developed. This suggests either a local or direct effect of estrogen on testes of specific genetic background, but does not rule out alteration in function of pituitary or other organs.

Cryptorchid environment may play an important role in Leydig cell tumor induction. Mice made surgically cryptorchid and receiving mild (nonsterilizing) doses of estrogen in food or from grafted ovaries developed 72-82% gross tumors. In unoperated animals, which received the same dose of estrogen, gross tumor incidence was 33%. In untreated cryptorchid animals, tumor incidence was 44%, but these were of microscopic nature. In cryptorchid animals tumors arise directly from Leydig cells initially present[55] in contrast to new Leydig cells that develop with estrogen induced tumors. Brown degeneration of the Leydig cells was not observed. Induction of tumors by cryptorchidism does not invoke any specific effect of ICSH for induction of tumor and raises the question of the role of ICSH in the process. The possible significance of seminiferous tubule degeneration, as it occurs in cryptorchidism, in relation to tumor development was studied by effect of x-ray on Leydig cell growth. Eschenbrenner et al[56,57] found that the apparent increase in interstitial cells accompanying and following exposure to x-ray was not related to degree of atrophy of seminiferous tubules so that tubule degeneration per se is not a stimulus to interstial cell hypertrophy and hyperplasia.

To further study the role of ICSH in tumor induction, testes from mice treated

with diethylstilbestrol and/or ICSH were transplanted before tumor development to estrogen treated mice. Subsequently, more testes from diethylstilbestrol treated mice developed tumors than from ICSH treated ones. Incidence in the latter was nearly the same as in mice from normal donors.[58] This helps to demonstrate that increased numbers of interstitial cells in itself does not increase the chance of tumor development. While this experiment does not point to a specific role for ICSH, it does not rule it out as a possible factor.

Experimental consideration has been given to the possibility of a direct effect of estrogen or other carcinogen on testes. Intratesticular implant of methylcholanthrene or benzypyrene produced no interstitial cell tumors but only 5% incidence of fibrosarcoma.[59] Gardner[59] found no greater induction of interstitial cell tumor by intratesticular implant of estrogen pellets than by parenteral injection of estrogen.

To elucidate the mechanism for induction of these tumors, attempts have been made to accelerate or retard the tumorigenic chain of events. If tumor induction is dependent upon an increased production of ICSH from the pituitary under influence of estrogen, it should then be possible to reduce the incidence of these tumors by inhibiting the production and release of ICSH.

Since progesterone has been shown to have as one of its actions the ability to reduce the production and release of ICSH from the pituitary[60,61] Blivaiss et al[62] compared the time of development and incidence of interstitial cell tumor induction in strains A and BA(C) mice which were treated with estrogen to those treated with estrogen and progesterone. They found that the first group showed a greater incidence of tumors and a younger age of appearance of first tumor than in the second group. This showed that progesterone can delay the induction and reduce the incidence of tumors, and supports the idea that increased ICSH may be a factor in the production of these tumors. Recently Andervont et al[63] have also reported that

progesterone somewhat retarded the occurrence of tumors. Hooker and Pfeiffer[24] found that androgens also retarded induction of interstitial cell tumors by estrogen in mice.

Hooker[47] reported that after cessation of 6 months' subcutaneous treatment with estrogen, testes returned to normal. Andervont et al[64] have found that tumor induction did not require continuous estrogen treatment. They observed that tumor development would occur in BALB/C mice several months after cessation of a 4-6 month period of treatment with diethylstilbestrol. This indicates that tumor development could occur after an adequate change in the cells or cellular environment without further estrogen administration. Blivaiss et al[62] also found that the greater the dose of estrogen in the early stages of development, the greater is the incidence of tumor production. If the estrogen dose is high in the first few months of treatment, but is later reduced to a non-sterilizing level, there appears to be no effect on tumor incidence. However, if the estrogen dose is low throughout the experiment, the tumor incidence is reduced. In another experiment, Andervont et al[64] found that if diethylstilbestrol pellets were removed after 1-7 months of administration, but before tumors were apparent, 5-9 months later, when treatment was reinstituted, 50% of mice developed tumors within 4 months. Controls, without pretreatment, developed 7% tumors in 4 months. When pellets were removed after testes were tumorous, about 50% regressed to normal size, while the others continued to grow. They described seven different growth patterns, ranging from persistent growth to regression. When treatment was reinstituted, most regressed tumors recurred within a month. Implantation of testosterone or progesterone did not affect the rate of recurrence of tumors that had regressed.[45]

Tumor Transplant

At first it appeared that interstitial cell tumor transplants would only grow in recipient mice supplied with exogenous or endogenous estrogen,[24,32] but this

appears now to be related to estrogen dependence or autonomy of the tumor. Tumors composed of small cells (i.e., older tumors) can be more readily transplanted. Paradoxically, the dependent tumors metastasize, although they are relatively benign histologically. This is unexpected since metastasis is usually a primary indication of autonomy. Later, Bonser[33] successfully transplanted a tumor to normal males. Gardner[65] found that tumors would not grow in the absence of estrogen but persisted in a latent state. With the implant of stilbestrol pellets in the host at 50-204 days after grafting, the tumor resumed its growth. Jull[66] found the latent period of tumor transplant longer in normal female than in normal male or gonadectomized male or female mice. He also observed that administration of stilbestrol or estradiol to the host prolonged the latent period while triphenylethylene (a synthetic estrogen) had no such effect. Fragments of an interstitial cell tumor grew successfully when grafted intrasplenically next to estrogen pellets but not in the presence of cholesterol pellets.[58]

Andervont et al[64] found that 8 of 10 primary tumors that developed in BA(C) mice at 1-12 months after estrogen treatment was discontinued were autonomous in the initial grafts. Thus, tumors formed after cessation of treatment showed a greater incidence of autonomy upon transplantation than tumors formed in animals under constant estrogen treatment. Induced tumors, though very dependent upon estrogenized hosts for early passages, show a strong tendency to become autonomous during the course of several transplants.

To elucidate growth requirements of this tumor, Huseby[58] studied the conditions necessary for transplant of 6 tumor lines. He found that all grew in estrogen-treated animals, but doubted that there was any direct stimulatory effect of estrogen on testes. Some grew in castrated, untreated animals, which indicated that estrogen action is not the only stimulating factor. In three tumor transplant lines, administration of pituitary ICSH produced tumor growth in intact males

but not in castrate animals, suggesting that stimulatory effects of administered ICSH are mediated via gonads. In three types of androgen producing tumors, treatment with gonadotrophin increased hormone production, while treatment with progesterone decreased it. This suggests that hormone production by these neoplasms is still under pituitary regulation.

Leydig Cell Tumors in Man

Over 60 cases of interstitial cell tumors of testes have been reported in man. These were divided into 32 post-puberal benign tumors, 8 post-puberal malignant tumors,[67–72] 18 prepuberal benign tumors, 1 prepuberal malignant tumor and 4 bilateral tumors.[73–75] Prepuberal tumors have been observed between infancy and puberty accompanied by precocious sexual development, gynecomastia, increased bone age and increased body musculature. In a group of younger children, all cases of Leydig cell tumor showed precocious puberty, while in older ones seven showed gynecomastia.

Gilbert and Hamilton[76] and Blundon et al[77] report that about 11-32% of patients with this tumor have a history of decreased spermatogenesis, atrophic testes, or cryptorchidism, although the tumorous testis is not always the cryptorchid one. The other testis may appear normal at removal of the tumorous one, but usually becomes tumorous even after being lowered into the scrotum. However, data does not justify the idea that the ectopic state is necessarily related to carcinogenesis.[78]

Mancini et al[79] believe that testicular Leydig cells in the human are of connective tissue nature and of mesenchymal origin. They produce reticular fibrils, as do intertubular and tubular connective tissue. With aging, the Leydig cells show an involution into fibroblasts.

When 16 humans were placed on long-term estrogen therapy,[80] the testes showed a denegeration of Leydig cells with formation of "fibroblast-like" cells and an increase in reticular fibers. These changes are believed due to a decrease

in ICSH. Occasionally there appeared normal immature Leydig cells in adenomatous clusters with vacuolated or metachromatic cytoplasm and hypertrophic nuclei suggestive of Leydig cell tumors of mice.

In a study of human spontaneous Leydig cell tumors, care must be taken to differentiate tumors of interstitial cells of the testes from those originating from adrenal cortical remnants in testicular tissue. Morphologically, this differentiation is extremely difficult. The finding of crystalloids of Reinke in the tumor cells is the most reliable morphological evidence of their Leydig cell origin, but these are rare in neoplastic cells. Crystalloids of Reinke are seen only in man, the opposum and the deer. Metastases of Leydig cell tumors are rare but may appear years after a histologically benign tumor is removed.

Hormone Secretion by Tumors

Mice bearing primary estrogen induced interstitial cell tumors show evidence of androgen secretion, as seen by enlarged seminal vesicles and prostate glands.[23,24 et al] The secretory ability persists after transplant of estrogen induced or spontaneous tumor. Secretory ability appears greatest when the degenerated Leydig cells have been replaced and the tumor is composed of large normal-appearing cells. Activity is least when the tumor is made up of small hyperchromatic cells. Thus, male accessory reproductive organs may appear enlarged in animals with a young tumor and atrophic in animals with long-established tumors. Grafts of spontaneous interstitial cell tumors in RF strain mice produced masculinization of castrated males, adrenocortical atrophy and deciduoma formation in females without uterine trauma.[81] Steroid metabolites in the urine of tumor hosts showed a 28-fold increase in excretion of androsterone over normal, a 50-fold increase in excretion of uncharacterized 17-ketosteroids, and an absence of etiocholanolone.

Exogenous ICSH, such as pregnant mare serum or anterior pituitary extract, increased secretion of androgen by transplants of spontaneous tumors[82] and several estrogen induced tumors.[58] However, androgen secretion was inhibited by progesterone administration.

Some estrogen-induced Leydig cell tumors appear to secrete estrogen and progesterone.[39 58] High levels of estrogen were found in the urine of a male dog with a metastasizing interstitial cell tumor.[83]

The study of enzyme systems in the biosynthesis of steroids by estrogen-induced intersitial cell tumors in mice shows a correlation between side-chain splitting and C-17 hydroxylase activity and *in vivo* masculinization.[84] No correlation was found between these tumors 3-B-ol dehydrogenase content (an enzyme probably necessary for synthesis of both gonadal and adrenocortical hormones) and biological effects of such tumors.[84,85] Two Leydig cell tumors with weak masculinizing effects converted progesterone to phenolic compounds, probably estrogens.[58,85] Of special interest is the discovery of the ability of some tumors to hydroxylate at C-21, an essential step in the synthesis of corticosteroids, and usually considered to occur only in adrenocortical tissue.[84] During the process of tumorigenesis and serial transplantation, loss of steroid biosynthetic enzymes occurs in a more or less random fashion. This loss does not necessarily reflect either the growth rate or degree of dependency of the resultant tumor.

Gynecomastia has been observed in 10 cases of interstitial cell tumor in which 4 were children. Elevation of estrogen excretion was recorded in five cases.[71,72]

Rowlands and Nicholson,[86] Stewart et al,[87] and Masson[88] reported evidence of increased gonadotrophin excretion and androgen secretion by interstitial cell tumors of humans. Development of sexual precocity in prepubertal boys due to Leydig cell tumors has been reviewed by various authors (see above). After operative removal of the tumor, there was a decrease in excretion of 17-KS and partial regression of precocious development in the case of prepuberal boys.[89] In cases of tumor with gynecomastia, there may

be a suppression of 17-KS excretion which becomes elevated after removal of the tumor. In others, both 17-KS and estrogen excretion may be elevated after surgery.[72] Herrmann[71] found an increase in excretion of total 17-KS as well as androsterone and etiocholanone after removal of a feminizing tumor, but little change in 17-OH-CS, which suggests an increase in testosterone secretion. In cases of masculinizing tumors, the ratio of Beta-17KS to Alpha-17KS was elevated before tumor removal and decreased afterwards.[90] The ratio of Beta to Alpha can be used to differentiate between interstitial cell and adrenal rest tumors.

Measurements of urinary FSH and HCG in both pre- and post-pubertal cases of interstitial cell tumors have yielded data of normal or below normal range.[91]

Venning et al,[92] in a case of tumor of human testes, found elevated urinary gonadotrophin and increased 17-KS, due mainly to androsterone and etiocholanolone, with no proportionate increase of dihydroepiandrosterone, a compound originating in the adrenal cortex. Similar observations have been reported by Hoffman[93] in an adult and Cook et al[94] in a child. This rules out increased 17-KS from the adrenal cortex. With administration of testosterone to a patient by Venning,[32] approximately equal amounts of androsterone and etiocholanolone were excreted after tumor removal compared to a 4-fold greater excretion of the former than the latter before removal of the tumor. This raises questions as to 1) whether testosterone was being secreted by the tumor, and 2) whether the metabolic pathway of testicular secretion was altered.

Baggett et al,[95] in the study of a tumor in a boy 5½ years old, found 11-oxygenated 17-ketosteroids, indicative of an 11-B-hydroxylase system previously thought limited to adrenal tissue. This raises questions as to whether 1) in spite of pathological diagnosis of interstitial cell tumors, adrenal tissue was contained in the tumor, and 2) does normal testis contain 11-B-hydroxylase, which is increased in a tumor. It may be that the 11-B-hydroxylase of the testis may be specific for

C_{19} but not for C_{21} compounds, since testosterone, but not progesterone, were hydroxylated by this enzyme.

Because of the homology between testes and ovarian medulla, it is of interest that Leydig cell tumors of the ovary have been reported to produce increased excretion of 17-KS in only 2 of 10 cases thus studied.[96] However, masculinization is a common characteristic of 14 cases reported in the literature.[97]

Summary and Conclusions

While one cannot positively state that the etiology of the spontaneous Leydig cell tumor is similar to that of the experimental tumor, the experimental approach provides a means for analyzing possible means of its induction. It appears that whatever the mode of induction, the original hyperplasia does not proceed uninterrupted into neoplasia. Rather, the normal Leydig cells are replaced by a new generation of cells. In these cells there appears to be an alteration or derangement of the mechanism that normally controls mitosis and differentiation. Consequently, there occurs tumor development. The similarity in appearance of Leydig cells in tumors occurring in various mammalian species suggests the existence of some fundamental change in cell function or regulatory mechanism for cell growth.

While estrogen administration to mice has produced interstitial cell tumors, this procedure has been unsuccessful in rats. On the other hand, procedures which result in an increased gonadotrophin secretion, such as intrasplenic transplant of testes, have been successful for the induction of tumors in rats but not in mice. This may indicate that, in mice, the effect of estrogen as well as some change in pituitary function is needed, while in rats only the change in pituitary function is necessary.

The limitation of tumor induction to certain strains of mice indicates a genetic factor in determination of susceptibility to this process. The commonly accepted susceptible mouse strains are related to each other,[98] while strains resistant to

estrogen-induced interstitial cell tumor, such as the C_3H, CBA and C_{xi} strains also have a common ancestry.[99] The importance of genetic factors is also shown by reports that tumor induction is dependent upon the type of estrogen used. Some strains of mice produce tumors when treated with one or more estrogens, but not with others. There is a need for a study to determine the metabolic products of the various estrogens in relation to their tumor-inducing ability in the tumor-sensitive and tumor-resistant strains.

There is a great variability in the growth patterns of interstitial cell tumors. This may reflect the fact that many general and local factors influence the progression of the tumor. The action of estrogen on the hormonal, genetic, embryologic and metabolic factors that control differentiation of the Leydig cells, and the function of pituitary secretions in the induction of this tumor still need clarification. While pituitary or chorionic gonadotrophin preparations alone do not produce a tumor, their administration in combination with estrogen enhances or accelerates tumor formation. The role of gonadotrophin appears significant in view of retardation in tumor development following administration of anti-gonadotrophin or anti-ICSH serums or progesterone.

Observation in estrogen-treated, tumor-susceptible mice of a temporary elevation of pituitary ICSH above its estrogen-depressed level, though still below normal, is most interesting, since it corresponds to a period of development of Leydig cell tumor. It is possible that this temporary rise in ICSH, plus a possible direct action of estrogen on testes, may trigger differentiation of tumor cells from primitive mesenchymal tissue in the testis.

Cryptorchidism in the mouse appears to reduce the dose of estrogen needed for tumor development but the effect of cryptorchidism on tumorigenic processes is not clear. While it is possible that atrophy of seminiferous tubules may play a role here, similar results are not obtained if tubule degeneration is induced by x-ray. Cryptorchidism is not known to affect pituitary function or release of humoral substances regulating Leydig cell growth.

Study of host-environment requirements for transplantation of these tumors have shown that the young tumor is estrogen dependent. In contrast, a well-established tumor, or one that has gone through several transplants, becomes autonomous. Transition from hormone dependence to autonomy is also shown by maintenance of tumor growth in estrogen-treated animals after discontinuance of estrogen treatment.

Several authors have discussed the relation of atrophic or cryptorchid testes to tumor development in man. However, there has not been any clear demonstration that ectopic testes have a greater incidence of interstitial cell tumors. It is of interest that the administration of estrogen to adult men has produced changes in the interstitial cells resembling those observed in mouse testes after estrogen treatment.

During hypertrophy and hyperplasia, and early stages of tumor development, mouse tumors secrete androgens. Androgen secretion can be enhanced by administration of gonadotrophins. Some estrogen-induced mouse tumors, as well as spontaneous tumors in dogs, horses and men, have produced gynecomastia and elevated estrogen excretion in the urine.

Mouse tumors have been shown to have the ability to hydroxylate 17-OH-progesterone at C-21, a reaction originally thought to occur only in adrenocortical tissue. This may indicate a relation between interstitial cell tumors and adrenal cortex tissue, or a modification of the steroid biosynthesis enzymes of the tumor as a result of tumorigenesis.

Human prepuberal interstitial cell tumors have been shown to result in precocious sex development or gynecomastia accompanied by an increased excretion of 17-ketosteroids or estrogen, respectively. In the case of masculinizing tumors, it is of special significance that the increase in excreted 17-ketosteroids was due mainly to the beta products of testosterone metabolism (androsterone

and etiocholanone). After surgical removal of the tumor, there was a decrease in these products and a partial regression of secondary sexual characters. This would confirm the testicular origin of the elevated beta 17-ketosteroids before surgery.

Future Directions

The mechanism for experimental induction or spontaneous development of interstitial cell tumors still needs clarification. In the case of experimental tumors, information is needed on the metabolism of estrogens, adrenal function and pituitary secretions during the induction process. In the case of spontaneous tumors, information on the endocrine function of the tumor, adrenal and pituitary are very important. While the procedures for collecting these data are time-consuming and tedious, their performance is necessary for a better understanding of the problem.

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THE SUICIDAL PATIENT IN GENERAL PRACTICE*

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Suicide is defined as the successful attempt of an individual to take his own life. In the field of major psychiatry, the problem of suicide is of central importance. In some of the more severe psychiatric disturbances, suicide is one of the ever present problems. One of the chief reasons for the hospitalization of psychiatric patients is the lessening of the risk of suicide. In the field of minor psychiatry, as practiced by the general practitioner, there are suicide risks also. A practitioner must have some general understanding of the situations and conditions in which it is possible to discount the risk of suicide, and of those in which the risk is serious or urgent and in which it is necessary to share the responsibility with a psychiatrist or to recommend hospitalization.

To begin with, certain attitudes of the general practitioner should be mentioned. One of them is the attitude that all individuals with personal difficulties are suicidal, and that the physician should avoid dealing with personal problems to protect himself from involvement in an actual suicide. Many physicians are much too afraid of contact with any psychiatric problems because they take much too

seriously the suicide risk. On the other hand, some practitioners are much too careless about the problem of suicide risk. They may feel that nothing can be done about it, that there are no criteria for judging the degree and kind of risk, and that no human being, even though he is a physician, has the ethical right to keep another human being from doing what he wants to do when he wants to do it. Both of these attitudes, of undue anxiety and of undue carelessness, are mistaken. Not all patients with personality difficulties are suicidal. A few are; most are not. In some situations the risk of suicide is very great and calls for emergency activity on the part of the physician, while in other situations the risk is so small that the practitioner need have little or no anxiety. Although as yet there are no sets of thoroughly trustworthy criteria of the intensity of suicidal risk or of its imminence, there are, however, some indications which are of value. As to the ethical problem, one need only say that the serious suicide risks are aspects of illness, during which the patient needs to be protected by the community, the family, and the physician.

In the minds of most doctors, there is a too close association between manic-depressive psychosis and suicide. When the problem of suicide is raised, most physicians think of the associated idea,

manic-depressive psychosis. It is more correct to have the two items linked closely in the other direction, i.e., the idea of manic-depressive psychosis should bring up the idea of suicide. Suicides do occur in the manic-depressive, but a large percentage of suicidal attempts take place in other conditions. The motivations for the suicidal attempt and the method of handling it are then quite different from what they would be if the suicidal attempt were part of a manic-depressive psychosis. The following is a discussion of some of the main conditions in which the problem of suicide may occur.

Normality

In our discussion of the suicide problem we must consider (a) actual suicides, (b) suicidal attempts, and (c) suicidal thoughts and impulses. In our civilization, actual suicides in normal and mature individuals seem not to occur. In certain other civilizations, actual suicides do take place in the setting of normality. For example, in Japan, individuals who were certainly normal and mature, in that culture, committed suicide when some venture was unsuccessful and when they felt disgraced. The suicide restored honor to the family.

In our civilization, suicidal attempts are probably nonexistant, or extremely rare, in individuals who are normal and mature.

Suicidal impulses and thoughts, however, are wide-spread in our civilization. It is probable that there are very few individuals indeed who go through life without some impulses, at one time or another, to commit suicide. This point is of importance for psychotherapy, since at times it may be necessary for the physician to assure a patient that the presence of a suicidal thought is not of itself an indication of a psychosis or of an impending psychosis. In the absence of other signs of disturbance, isolated suicidal thoughts are not to be taken seriously. An individual who is sufficiently normal and mature for all practical purposes may have in the course of his life an extraordinary variety of illogical thoughts and impulses. Occasional suicidal thoughts, occasional murderous thoughts, occasional thoughts of homo-

sexuality or of sexuality connected with animals and the like, may arise occasionally in the conscious thinking and wishing of individuals who are to a sufficient degree normal and mature.

Hysterical Personality

All physicians are familiar with the clinical entity called hysteria. It is the illness in which signs of physical disturbance are present when there is no physical disease to account for the clinical signs. The manifestations of hysteria are the expression of an attempt to solve, in physical terms, some emotional conflict. For example, an hysterical blindness may be the attempt on the part of the individual to solve a conflict between a strong desire to peep, to see forbidden sexual things, and the opposing pull of avoiding such behavior. Conscience, moral standards and fears of discovery and of punishment would be some of the forces standing in the way of the satisfaction of peeping desires. The individual, who, for some reason, is not able to solve the conflict between the impulses to peep and the controlling impulses in some constructive or healthy way, may develop an hysterical blindness as a solution. The solution consists in the fact that, if he becomes blind, the conflict disappears, because there is then no longer the possibility of indulging in the peeping. The blindness prevents the peeping, it lessens the temptation to peep, and it also is a punishment for the impulses to peep, along the lines of the exhortation that "if thine eye offend thee, pluck it out." Similarly, an hysterical paralysis of the hand may be the physical solution of a conflict about masturbation, which usually involves the use of the hand in sexual satisfaction, or it may be the solution of a conflict about the impulse to hit or to hurt someone.

It has also been found that there exists a particular type of personality make-up in hysteria. Hysterical individuals very frequently behave as if their goals in life were: (a) to be spiteful and revengeful, (b) to get attention, (c) to control the environment and people around them, e.g., by threats and gestures, (d) to be dramatic, and (e) to gain sympathy. Such goals develop out of deep-seated anxieties, conflicts and immaturities. Drives in

these directions are often exceedingly powerful in the hysteric individual, and may lead to a pattern of life that is directly opposed to the mature behavior that would lead to happiness or to lasting pleasures and values.

This particular constellation of personality goals (spitefulness, attention getting, etc.) may exist even when the hysterical, physical signs of illness are not present. It is possible, in fact it is fairly frequent, to find individuals who have this anxiety ridden, hysterical personality make-up without their ever having somatic manifestations of hysteria. The general practitioner may find that a significant number of his patients belong to this group.

The individuals in the hysterical personality group use many means to attain their goals. Temper tantrums and the prolongation of convalescence are two examples of the behavior which is developed to achieve these immature goals. The threat of committing suicide is another way, a powerful tool with which to influence their environment. The threat of committing suicide, or an actual suicidal attempt, acts powerfully in the direction of getting attention for the individual, of placing him in the center of the stage. Often it is a manifestation of spite or revenge, or of getting even with someone. It frightens others into submission. It satisfies the individual's urge to dramatize the situation. It gains sympathy. The girl whose boyfriend begins to pay attention to another girl may make a suicidal attempt largely by way of revenge for the jilting. The impulse, often conscious, is to be revenged on him, to get his attention, to frighten him into coming back to her, to express her dramatic sorrow, and to be an object of pity and sympathy. She may believe that she is making the suicidal attempt because she is broken-hearted or because she has lost the most important thing in her life. Those surface reasons are merely rationalizations, and the true reasons are to be found, with a little analysis, in the goals listed above.

Such an individual does not have a desire for death, and the suicidal attempt is often impulsive and quickly regretted.

The chances of success in such a suicidal attempt depend largely on the chance factors that are involved. If the suicidal gesture is made with iodine, there is no danger. But if the suicidal attempt is made with bichloride of mercury, there may be great danger. The method used is chosen not so much in terms of its actual danger, but in terms of what is available at the moment of the impulse, and in terms of what the individual has read about in the newspapers.

The suicidal attempts of the hysteric are probably the most frequent variety of suicidal attempts. In the receiving ward of a large city hospital, a large percentage of individuals who are brought in after suicidal attempts belong to this group. In general it may be said that the suicidal attempts of hysterics occur frequently, that they are not very serious, and that the patient need not be hospitalized unless there are other indications for hospitalization.

It is important that, in dealing with such suicidal attempts, *the physician not become fearful or anxious*. A demonstration of anxiety on the part of a physician adds to the power of the suicidal threat or gesture. Since the essential purpose of the attempt is to affect others by it, the effect on the physician is important. If the patient is successful in reaching his goal, through the suicidal attempt or gesture, of controlling a doctor or of getting much attention or the like, the chances of a second use of such a tool will increase.

Such a suicidal attempt is essentially an indicator of unhappiness and maladjustment, and of a need for psychotherapy. If the individual has developed such neurotic goals, if he has to have recourse to such immature techniques for satisfactions in life, one can be sure that there are fundamental difficulties in his adjustment, either in the form of externally caused unhappiness or of inner problems or conflicts. Further, such goals are almost always self-thwarting and self-stultifying. The girl who succeeds temporarily in bringing back the boyfriend by a suicidal gesture often will find that, within a short period of time, he will gradually ease himself out of the situa-

tion with her, when he can do so without precipitating another suicidal attempt with its publicity and implied criticism.

The physician in such a situation should not give way to his own reactions of revenge toward the patient. The physician may feel that the patient is doing him a dirty trick by attempting suicide after he has tried to help her, and the physician may become angry or spiteful in turn. Such a reaction is wrong on two counts. First, it may be what the individual has wanted. The patient may have been essentially provocative in the suicidal attempt, hoping to provoke attention from others, including the doctor, even though that attention consists only of criticism, punishment or anger. The doctor may simply be falling into the role which unconsciously has been assigned to him by the patient. Second, such a reaction of punishment and criticism on the part of the doctor is wrong because he misses the boat. The patient who makes such an attempt is deeply and fundamentally in need of understanding and treatment, not of punishment or domination. The patient's neurotic goal may be to force other individuals into the position either of submitting to him or of punishing him, but this neurotic goal need not be the real goal of the individual. The physician does best by preserving the traditional role of the physician, that of being a good, understanding father figure, who does not approve of the shenanigans of small children, or of adult children, but who at the same time is not punishing and not destructive, who cannot be controlled or forced to submit, and who is willing to forgive and to hope for and to work toward a growing-up on the part of the child and of the patient.

Delirium

In delirium a number of individuals kill themselves. Perhaps in a true sense this is not a suicide, since it is not usually purposeful. But at least it is a death in which the individual dies as a result of some action of his own.

The fact essentially is this: that, in delirium, whether it be cardiac, alcoholic, febrile, or other, individuals may become so confused and so disoriented that *they*

must not be placed in a situation in which some chance activity on their part may lead to their death. For example, a delirious patient may, if unwatched, wander around the hospital ward and step through a low window thinking that it is the door to the toilet. If the window happens to be far enough from the ground, he may drop to his death or at least to serious injury. The practical point here is that individuals who are delirious should, if possible, be placed in a ward or in a room on the first floor of a hospital. If such care is not possible, a nurse should be in constant attendance and all the windows and doors should be guarded.

Delirium is often present at night in cases when it is not present during the day, and the physician may not detect it in the course of his daily rounds. In this case, nursing notes are very helpful. The manifestations to be watched for are: (a) disorientation, (b) fear, (c) confusion, (d) poor comprehension, (e) hallucinations, and (f) illusions. In most delirious conditions, psychologic factors play a definite role. A patient's insecurity in the hospital situation, his fear of the effects of an operation, his lack of understanding of the purposes or of the facts of the operation, or of the postoperative procedures, all combine to produce feelings of uncertainty, which predispose to the development of delirious reactions or add to their intensity.

The undue use of medications, in many cases routine dosages of psychotropic drugs, particularly those which tend to dull the sensorium, may add to the possibility of the development of a delirium. Most of the psychodysleptic drugs, being onirogenic and hallucinogenic, do produce oniric psychoses. These effects may also cause acute depressions in susceptible individuals, and result in actual suicidal attempts.

Psychotherapy is an essential part of the treatment of delirious reactions and of the prevention of self-harm that may be associated with the delirium. Firmness and clarity on the part of the physician, the constant attendance of a reassuring nurse, and the feeling, on the part of the patient, of having someone on whom

he can rely definitely and surely are effective measures.

It is distinctly conceivable that a delirium may end with self-harm and suicide. This essentially is the result of bad conscience over past experiences and the need for punishment to alleviate the pangs of guilt. A delirium may provide a sufficient release of inhibition to permit the expression and the carrying through of tendencies which ordinarily are inhibited.

Acute Alcoholism

The last sentence, with its emphasis on tendencies that appear when inhibition is released, leads to a statement of the suicide risk in acute alcoholic intoxication. When an individual is intoxicated, there is a rather marked release of the usual inhibitions. Aggressive social behavior, unusual sexual activities, talkativeness, boastfulness, and many other tendencies, of which the individual ordinarily would not permit expression, may reach expression when the individual has dissolved some of his controlling forces in alcohol.

A certain number of suicidal attempts will take place when an individual is in a state of alcoholic intoxication. It may be that the individual has suicidal tendencies which ordinarily have been inhibited and controlled and which are now released when the inhibition is dissolved. Also, the individual, through the release of inhibition due to alcoholic intoxication, may have surging upward in him certain other impulses which ordinarily he had kept deeply hidden from himself. The presence of such impulses, and the possibility of their being put into action, may arouse in him strong feelings of guilt or fear. The suicidal attempt may be the expression of a severe conscience reaction to such unacceptable impulses. In the opinion of many workers, the alcoholic tries to kill himself with his booze, and, in the case of cirrhotics, often succeeds.

Schizophrenia

The explanation of a suicide attempt in schizophrenia would have to include an explanation of the deeper psychodynamics of the particular schizophrenic individual. Very simply put, we know that one of the very frequent manifestations of schizophrenia is auditory hallucinations. Further, one of the common manifestations of schizophrenia is that the individual feels under the influence of, or ordered by, forces outside of himself. Many schizophrenic patients hear voices ordering them to perform specific actions or not to perform others. A schizophrenic patient may hear voices telling him to mutilate himself or to kill himself, and under such circumstances an exceedingly severe suicidal attempt or self-mutilation may take place. For example, a schizophrenic patient may try to cut off his genitalia, because he has "sinned" with his genitals.

Such behavior is an extreme type of the dominance of one variety of primitive conscience, which is also found in many patients who are not schizophrenic. Such a conscience is built up in terms of the "talion law," which demands an eye for an eye and a tooth for a tooth, and which demands punishment of an offending organ. Death can result from complications of this self-mutilation as well as frank suicide. The physician cannot successfully treat this patient without expert aid.

Paranoid State

The essential manifestation of the paranoid state is a delusion, i.e., the mistaken idea, which the paranoid completely believes, that he is being persecuted or ill-treated by some individual, group, or force. Again, I will skip over the deeper psychodynamics of the paranoid attitude, and state merely in this connection that a certain number of paranoid individuals commit suicide in the attempt to escape persecution. The persecution, even though it does not exist, seems exceedingly real and painful to the patient and the result may be an attempt to escape through death. The general practitioner should not try to treat such a patient by himself, and should send for psychiatric consultation and press for ·institutionalization of the patient.

The Panic State

The general practitioner should be aware of the existence of panic states, because they involve dangers which may

lead to the need for hospitalization, and because at times they may be prevented or alleviated when the practitioner provides security and firmness for the patient. Panic states in individual patients can best be understood by pointing out some of the manifestations of the panic states of a group. When someone shouts "fire" in a theater, many people become panicky. Overwhelming fear is the central reaction. Some individuals may be so overwhelmed with fear that they are unable to move. Such a reaction is called "frozen panic." Other individuals may be so overwhelmed by fear that they go into states of enormous and intense overactivity. They may run to the nearest exit, knocking people down in their fearful rush, and smash up against a door, which would open toward them, only to close it more tightly. They may try to smash through a brick wall. They may kill others, or kill themselves, in this wild overactivity. Such a reaction is known as "panic excitement." These are examples of group panics, and of panic of individuals in a group, when there is an **external** cause for the overwhelming fear.

There are also individual panics. Individual patients may go into panic states when no one else is panicky and when there is no external precipitating cause for such a degree of fear. Such panic states occur essentially on the basis of an **internal** conflict over unacceptable impulses which have surged to the surface either spontaneously or in reaction to some recent trigger experience in the individual's life. The nightmare is a transient and realistically harmless example of such an individual panic. But a panic state may occur in full daylight with the individual wide-awake, and may last for several weeks or longer. The individual in such a panic state may be seriously disorganized and have a set of symptoms which are exceedingly difficult to distinguish from those of schizophrenia.

In a state of panic-excitement the individual may commit suicide. In part, this is the result of the submerging of his judgment, self-control and intelligence in overwhelming fear. In part, the panic itself and the suicide may be the concomitant results of the same conflict. For example, the panic and the suicide may both be on the basis of a conflict over homosexual impulses, or on the basis of a fear of castration, of death, or of being left alone, because of deep-seated aggressive impulses. Usually the physician need not concern himself with the cause of panic. But he should know of the existence of panic states, be able to recognize them when they occur, and know that such panic states almost always require hospitalization and the attention of a specialist.

The panic state should not be confused with an anxiety attack, in which there is some fear and the autonomic accompaniments of fear such as tachycardia, dilated pupils, elevated systolic blood pressure, etc. In the anxiety attack the individual is not overwhelmed. He complains of the fear or of its bodily accompaniments. He feels frightened and asks for help, and, in good part, he is able to discuss the situation with the doctor. In the panic state, however, the individual is overwhelmed by fear, and he behaves in accordance with the fear, e.g., he is frozen stiff and is unable to talk, or is in a state of great physical activity He does not have the ability to complain of fear or to discuss the situation or to cooperate with the doctor.

Depressive Phases of Illness Other Than Manic-Depressive

Many physicians are under the misapprehension that significant depressive states occur only in the form of manic-depressive reactions. This is a serious mistake, because in such conditions as paresis, pernicious anemia, etc., as well as in the face of many life experiences, depressive reactions of varying degrees of severity may occur. As part of such depressive reactions, suicidal attempts may take place. The risk should not be overlooked or ignored because the patient did not fit "the right picture."

Reactive Depression

The term "reactive depression" includes a number of groups. It can be used to include not only cases which are ordinarily called reactive depressions, but also to include neurotic depressions, hysteric depressions, depressions in compul-

sive personalities, etc. The physician need only consider three types of depression: (a) manic-depression (and involutional melancholia), (b) depressive reactions which occur in organic illnesses, such as paresis, and (c) depressive reactions which occur on a psychologic basis but still do not belong to the group of manic-depressives. These last reactions can be grouped into a catagory called reactive depressions.

In this group, the depression is usually milder than in the manic-depressive. In the reactive depression, the depression usually is in reaction to some actual event in the external world, whereas in the manic-depressive the depression often occurs when there is no disturbing event in the external world to precipitate the depression. In fact, some manic-depressive attacks occur when things are going well for the patient, or perhaps when he has an improvement in his external life-situation. In the reactive depression, the amount of depressive response is more in keeping with an external depressing situation. When the manic-depressive is depressed in response to some actual situation in his environment, the amount of depression usually is far out of proportion to the precipitating situation.

There is definite suicidal risk in many cases of reactive depression, but the suicidal urges usually do not have the severity or the persistence of the suicidal urges of the manic-depressive. In this general group, positive (supportive) psychotherapy on the part of the general practitioner is quite adequate in itself.

Manic-Depressive Psychosis

The manic-depressive psychosis is the condition which is usually linked with suicide. The intensity of the desire for death in these individuals is almost unbelievable. Their persistence in attempting to kill themselves is apparently an extraordinary contradiction of the biologic drive for self-preservation. In a deeper psychologic sense, even the suicidal attempt represents, in a very severely distorted fashion, certain urges in the direction of self-preservation, but the action itself is in the direction of death, not of life.

The practical issue for the general prac-

titioner is the preservation of the life of the individual during the depressive phase of the manic-depressive psychosis. During this phase the physician should hospitalize the patient. This period of hospitalization may only be for weeks or months, as the most serious suicidal attempts take place in acute depressive phases which are fundamentally temporary. Such individuals are usually grateful, after their recovery from the depression, to the physician who prevented their death during the attack.

In this connection, it is urgent that the physician realize that hospitalization does not guarantee the prevention of suicide; his recommendation to the relatives should not be that the patient should be sent to the hospital in order to prevent suicide. Rather his recommendation should be that the patient should be sent to a hospital in order to lessen the risk of suicide. Even in the best hospitals an occasional suicide takes place. It is not possible to keep such a patient under such strict observation that a slip-up in technique can always be avoided. A hospital which enforces extremely stringent observation probably is not doing the best job with all of its patients, because in such a hospital the repressive observation probably is a detriment to the recovery of other patients. However, close and adequate observation should be provided for patients with serious suicidal urges, and vigilance should be maintained as much as possible.

Psychoanalytic studies of the manic-depressive's drive toward death indicate that at least one very important component is the patient's unconscious conviction that he is a murderer, or has done great harm to some other individual or individuals. For the most part, this attitude is completely unconscious, and the patient is not aware of this fundamental conviction. It is to be noted that manic-depressive individuals are not murderers and have not been murderers, and that the idea of being a murderer is based on some past fantasies or impulses. Further, the manic-depressive has an extremely severe set of standards and conscience reactions, which in psychoanalytic terminology is called a severe superego. Such

an individual reacts to his unconscious conviction of being a murderer with the feeling that he should have the just desserts of murder, i.e., execution. He acts as if he were prosecuting attorney, judge, and jury in his own trial, and is then to be the executioner in his own death. The suicide of the manic-depressive individual is essentially a boomerang of homicidal impulses. The suicide is an attempt to satisfy the demand of the conscience, of the law of an eye for an eye and a tooth for a tooth, and, here, a death for a death. He can only achieve peace and serenity, atonement and absolution, and, in a sense, life, through death.

Danger Signals of an Impending Suicidal Attempt

A Deep Mood of Depression

This is a danger signal which cannot be described simply or in quantitative terms. It is based on one of those inexact estimates which it is necessary to make in many aspects of the practice of medicine, particularly as it relates to psychiatry. The ability to make such judgments as to the depth of a particular problem depends largely on experience and the art of medicine. The physician must decide if he is dealing with a mild reaction of depression or a deep-going reaction of depression. To caricature the problem for the sake of clarity, I will say that the physician should not pay much attention to the risk of suicide in a friend who said, casually, that he was feeling rather depressed, rather blue, and felt discouraged, and of whom the physician's observation was that the friend was only a bit downcast, but was still able and ready to carry on with conversation, work or pleasure.

On the other hand, the physician would take quite seriously the mood-statement of depression, blueness and hopelessness on the part of an individual who looked exceedingly downcast, who seemed, as the result of the low spirits, to be so "down" that he was hardly able to move, or so restless that he was unable to sit or to avoid picking constantly at his skin. Facial expressions, bodily posture, and the feeling that the individual was really in the depth of a "down" mood make the physician sense that he might be confronted with a serious problem. Further, the physician will take more seriously the suicide risk in an individual who has been depressed for some time than that

in an individual who has been depressed for only a day or two. All individuals have mood swings and normal individuals may have blue hours or blue days. Mood swings are somewhat more marked in neurotic individuals than in the normal. In the manic-depressive, the blueness is much more intense and much more lasting.

Concealment of Thoughts About Suicide

To a certain degree the physician can be guided by the fact that a great deal of talk about suicidal impulses, particularly if the talk is dramatic, is not so frequently associated with serious attempts as is the absence of talk about suicide. This is by no means an absolute rule. Many deeply depressed individuals who have serious urges in the direction of suicide, and who may soon make suicidal attempts, will talk about the suicidal thoughts to the physician, and at times even talk in a slightly dramatic fashion. But, frequently, patients who are deeply depressed will never mention the suicidal idea at all and yet be in imminent danger of making a suicidal attempt of a serious sort.

The physician should know that every individual in a deep depression thinks of suicide, even though he never mentions it. The physician must take seriously the risk of suicide if he is sure that the individual is in a deep depression, whether the patient mentions it or not. On the other hand, the physician need not take as seriously the risk of suicide if the patient talks a great deal about suicide in a very dramatic fashion, and if he seems to be watching the physician's re-

action when suicide is mentioned, apparently trying to see if the physician is frightened or impressed.

Autonomic Signs of Deep Depression

Perhaps the most reliable indicators of the depth of a depression, and of the associated serious risk, are to be found in a group of clinical phenomena which is variously labeled as the biologic, vegetative, somatic or autonomic accompaniments of depression. They are: (a) persistent loss of appetite, (b) serious loss of weight, (c) persistent insomnia, (d) persistent constipation, e) cessation or diminution of menstruation, (f) loss of sexual desire or potency, and (g) any unaccountable deviation in visceral function. In a deep depression there usually are to be found a number of these manifestations. If a given patient seems to be quite deeply depressed and in addition has several of these symptoms, the risk of suicide is very definite and should be treated quite seriously even though it is not mentioned by the patient. One would not take too seriously a blue mood in which an individual is depressed for several hours and unable to eat or stays awake for a good part of one or two nights. One would take quite seriously the suicide risk in a patient who showed a persistent depression, and over a period of time had serious difficulties in sleep, appetite, weight, etc.

Early Morning Dangers

It is a clinical observation that the risk of suicide is somewhat greater in the early morning hours. This may be based on fundamental physiologic factors, e.g., the lower temperature, lower blood pressure, and, perhaps, the lower level of what may be called life-forces in the early morning. It may be that the early morning danger is essentially based on psychological factors, e.g., the early morning feeling of horror of having to face another day of depressive suffering. Again this is essentially a problem of major psychiatry and largely of hospital psychiatry, yet again it is of importance to the general practitioner in dealing with those depressed patients whom he is forced to treat.

Depressive Delusions

The diagnosis of a deep depression, and consequently of a serious risk of an impending suicidal attempt, is made more probable by the existence of definite delusions with the depression. Most individuals who are depressed at all feel rather unworthy, inferior, and guilty. In some individuals in deep depressions such ideas reach the point of actual delusion-formation, i.e., of actual belief in obviously incorrect ideas. For example, a deeply depressed individual may believe that there is a complete separation of his stomach from his intestines, so that his intestines have actually dried up, or that his wife is contemplating a divorce after a brief spat when this is not true. The existence of such a definite delusion increases the risk of a suicidal attempt.

Past History of Other Suicidal Attempts

As in the sizing up of other medical conditions, obtaining an adequate past history of the individual's illness is of real service. One is able to get some idea of the course which the present reaction is likely to take by obtaining from the patient, or from the relatives, a history of similar past attacks. If one is dealing with an individual who is somewhat depressed, and discovers from the patient's story or from the relative's story that the patient has had similar attacks in the past, which then went on to a greater intensity with serious suicidal attempts, then one must take the present situation as having the definite possibility of repeating the course of the previous attacks.

The Recovery Stage Danger

It is a clinical observation that in some deep depressions suicidal attempts are more frequent in the stage of recovery than they are during the depth of the depression itself. It may be that in many depressions the patient, during the depth of depression, with strong impulses to suicide, is so slowed down in his activity that he is unable to carry through the behavior that would be necessary for a suicidal attempt. In the recovery stage, when greater activity is possible, there may be a strong urge remaining in the direction of suicide, which may then be acted out.

The problem really belongs in the field of major psychiatry, and consequently is more important for the psychiatrist than the general practitioner. However, the general physician should also be familiar with this problem, as it is occasionally necessary for him to take care of an individual in a moderately deep depression because of a family's refusal to consult a psychiatrist, accept psychiatric hospitalization, or because a psychiatrist is not available. A practitioner should avoid assuming responsibility in such circumstances, if it is humanly possible, but if he cannot, he must be sure not to relax his vigilance simply because the patient begins to show some improvement.

Absence of Manifestations of Hysterical Personality

The suicidal attempts of the manic-depressive are serious and persistent, but the suicidal attempts of the hysterical personality are usually not so serious nor so persistent, with the danger in the latter case arising essentially out of accidents or the patient's choice of a dangerous technique. If the individual talks of suicide in a way that gives the physician the feeling that the individual is quietly desperate, rather than melodramatically desperate, the risk probably is greater. If the individual does not seem to be behaving in order to get attention, does not seem to be inclined to arouse sympathy, and does not seem to be particularly spiteful or revengeful or threatening, the risk of suicide is greater. However, one should remain wary of the patients who seem to be in-between cases. There are some individuals who are seriously depressed and yet have, to a certain degree, some hysterical tendencies. Unfortunately there are many unclear cases, and the physician can only use his judgment in estimating the suicide risk.

Absence of Feelings of Affection

In psychoanalytic terminology this point has to do with the breakdown of the individual's capacity for positive sentiments, i.e., the breakdown of his ability to have positive feelings of affection, which, as transference, establishes confidence in some new helpful or trustworthy figure, e.g., a physician. In the depth of a depression, the patient's interest largely has been withdrawn from outside people or objects and is concentrated on himself. Further, in a deep depression there is so much conflict, guilt feelings, and unconscious hatred that sentiments of affection are felt or expressed only with great difficulty. The physician's estimate of danger in a situation should be increased when he feels that there is a coldness, a withdrawn self-centered attitude, and a loss of friendly feelings on the part of the patient. In such cases there seems to be a deep chasm between the patient and his previously loved ones or between the patient and the doctor. An increase in the tendency to brood and to be alone may indicate an increase in the withdrawal of friendly contact with the world.

Increased Tension

An otherwise unexplained increase in pulse rate or of pulse pressure may be a sign of increased tension and anxiety. This and other evidences of tension, e.g., tense facial expression, should be taken as a danger signal.

Unreality Feelings

It has been noted that severe feelings of unreality are often present in individuals who make suicidal attempts. Many normal individuals occasionally have such feelings, and they are of no consequence if only occasional and isolated. But frequent feelings of unreality, combined with depression, constitute a danger situation. In other words, the individual who feels unreal or estranged from the world, or feels that the world is changed or unreal, or that it is flat and lifeless is in a dangerous state.

Other Danger Signals

In psychoanalytic practice there are other phenomena which indicate the imminence of a suicidal attempt, e.g., evidence of the presence of an extremely strong unconscious hatred for which the individual seems to have found no other solution except to turn it on himself. Such signals, however, are of little or no use to the general practitioner.

Role of Physical Disease

In my discussion of suicide I have made no mention of serious physical disease, chronic disease, or pain as being factors in the production of suicidal attempts. A search of the literature based on clinical experience reveals that serious pain and serious physical disease do not increase the suicide risk substantially, or in fact lead to much of a suicide problem. The risk of suicide is not a serious one in chronic disease hospitals. It is true that any frustrating experience may act as a trigger to set off a variety of psychiatric reactions, including a suicidal attempt, especially in prone individuals, but it can be said that the actual physical disease or pain is a very incidental factor in the production of the reaction.

As a matter of fact, it now appears that physical disease and pain may lessen the suicidal risks in some cases. As mentioned earlier, the suicidal attempt often represents an extreme form of self-punishment and self-destructiveness, as a way of alleviation of conscience pangs about guilt-laden impulses. The conscience demands suffering in some form, self-imposed or inflicted by someone else, or produced by pain or disease. Often the conscience is not concerned about the source of the punishment, so long as there is punishment. Therefore, if disease and pain produce suffering, there may be a lesser need for self-inflicted punishment. The presence of serious physical disease or of pain may satisfy the conscience to a certain degree, and consequently lessen the need for self-punishment in the form of suicide. Similarly, many individuals have less of an urge in the direction of suicide when their life-situation is a painful or punishing or unhappy one. An individual may actually become less depressed and less suicidal when he has had a bad break in life, when he has been severely criticized, when he becomes physically sick, or is in pain.

Conclusion

If the general practitioner, after studying his patient in the light of the above list of danger signals, concludes that his patient is seriously suicidal, satisfactory management would call for collaboration with a psychiatrist or referral to a psychiatric In-patient service. The practitioner should avoid caring alone for patients who are seriously suicidal, unless he has no alternative. If the general practitioner, after studying the patient in light of the above discussion, is still uncertain about the suicide risk, he should arrange for psychiatric consultation for the patient. Nothing is more tragic, for the physician as well as for the patient and his family, than to have a patient take his own life after having been presented to the practitioner for evaluation and declared safe.

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VOLUME 21, NUMBER 4   JULY, 1961

CONTENTS

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